

09480389

(FILE 'HOME' ENTERED AT 10:28:52 ON 10 JUL 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 10:29:01 ON 10 JUL 2001

L1 9604 S GERMLINE AND MUTATION
L2 16414 S (IMMUNOASSAY OR ELISA OR ANTIBODY) AND SANDWICH
L3 2 S L1 AND L2
L4 2 DUP REM L3 (0 DUPLICATES REMOVED)
L5 2740218 S REVIEW
L6 657 S L1 AND L5
L7 8450 S MISMATCH REPAIR
L8 55 S L6 AND L7
L9 36 DUP REM L8 (19 DUPLICATES REMOVED)
L10 121 S L5 AND L2
L11 0 S L10 AND L7
L12 602114 S MUTATION
L13 1 S L10 AND L12
L14 1431263 S CANCER
L15 6 S L10 AND L14
L16 5 DUP REM L15 (1 DUPLICATE REMOVED)
L17 121 S L10 OR L16
L18 41 S L9 OR L16
L19 41 DUP REM L18 (0 DUPLICATES REMOVED)

0 L19 ANSWER 1 OF 41 MEDLINE
ACCESSION NUMBER: 2001355660 MEDLINE
DOCUMENT NUMBER: 21157259 PubMed ID: 11257106
TITLE: Deficient DNA ***mismatch*** ***repair*** : a common
etiologic factor for colon cancer.
AUTHOR: Peltomaki P
CORPORATE SOURCE: Division of Human Cancer Genetics, Comprehensive Cancer
Center, Ohio State University, 690 Tzagournis Medical
Research Facility, 420 West 12th Avenue, Columbus, OH
43210, USA.. peltomaki-1@medctr.osu.edu
CONTRACT NUMBER: CA67941 (NCI)
CA82282 (NCI)
P30 CA16058 (NCI)
SOURCE: HUMAN MOLECULAR GENETICS, (2001 Apr) 10 (7) 735-40. Ref:
75
Journal code: BRC; 9208958. ISSN: 0964-6906.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010625
Last Updated on STN: 20010625
Entered PubMed: 20010321
Entered Medline: 20010621
AB Hereditary non-polyposis colon cancer (HNPCC), the most common form of
hereditary colon cancer, is a syndrome of deficient DNA ***mismatch***
repair (MMR). Five, possibly six, human MMR genes have been
identified that, when mutated in the ***germline***, cause
susceptibility to this syndrome. To date, more than 300 different
predisposing mutations are known, mainly affecting the MMR genes MLH1 (
approximately 50%), MSH2 (approximately 40%) and MSH6 (approximately
10%). Genetically predisposed individuals carry a defective copy of an MMR

gene in every cell. Somatic inactivation of the remaining wild-type copy in a target tissue, typically colon, gives rise to a profound repair defect, progressive accumulation of mutations and cancer. Instability at short tandem repeat sequences, microsatellites, is a typical manifestation of MMR deficiency and apart from HNPCC tumors, occurs in approximately 15% of sporadic colon and other tumors. The majority of the latter cases are attributable to one particular MMR gene, MLH1, and unlike HNPCC, an epigenetic rather than a genetic mechanism plays an important role in the inactivation of this gene. The present ***review*** provides an update of the genetics of HNPCC and more generally, of cancer development driven by deficient MMR. Recent discoveries suggest that apart from post-replication repair, MMR proteins have several other functions that are highly relevant to carcinogenesis. Knowledge of the complex interplay between the MMR system and other cellular pathways allows us to better understand the phenotypic manifestations of HNPCC and other cancers with deficient MMR.

L19 ANSWER 2 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 2001122768 EMBASE
 TITLE: Carcinogenesis in the GI tract: From morphology to genetics and back again.
 AUTHOR: Redston M.
 CORPORATE SOURCE: Dr. M. Redston, Department of Pathology, Mount Sinai Hospital, 600 University Avenue, Toronto, Ont. M5G-1X5, Canada. mredston@mtsinai.on.ca
 SOURCE: Modern Pathology, (2001) 14/3 (236-245).
 Refs: 65
 ISSN: 0893-3952 CODEN: MODPEO
 COUNTRY: United States
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 005 General Pathology and Pathological Anatomy
 016 Cancer
 048 Gastroenterology
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB The genetic alterations in colorectal cancer progression are determined by one of two separate and distinct underlying pathways of genomic instability. The first pathway, chromosomal instability, is characterized by allelic losses and aneuploidy. The second pathway, microsatellite instability, is characterized by an abundance of subtle DNA mutations and diploidy. Although the genes causing chromosomal instability remain unknown, microsatellite instability is caused by inactivation of a DNA ***mismatch*** ***repair*** gene (predominantly MLH1 or MSH2). Microsatellite instability is present in 15% of colorectal cancers, and is diagnosed by analysis of tumor DNA from paraffin blocks and by demonstration of loss of ***mismatch*** ***repair*** protein expression in cancers. In addition to the unique profile of genetic alterations, colorectal cancers with microsatellite instability have distinct pathologic features and improved survival. Finally, cancers from most patients with hereditary non-polyposis colorectal cancer (or Lynch syndrome) have microsatellite instability due to ***germline*** mutations in the DNA ***mismatch*** ***repair*** genes. Identification of the microsatellite instability pathway has enormous implications for the clinical investigation and management of colorectal cancer patients.

L19 ANSWER 3 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 2001107146 EMBASE
 TITLE: Microsatellite instability: Application in hereditary

09480389

AUTHOR: non-polyposis colorectal cancer.
Saletti P.; Edwin I.D.; Pack K.; Cavalli F.; Atkin W.S.
CORPORATE SOURCE: Dr. P. Saletti, Ist. Oncol. della Svizzera Italiana,
Oncologia Medica, Ospedale S. Giovanni, Bellinzona 6500,
Switzerland. oncosg@siak.ch

SOURCE: Annals of Oncology, (2001) 12/2 (151-160).

Refs: 139

ISSN: 0923-7534 CODEN: ANONE2

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Colorectal cancer (CRC) is a significant cause of mortality in Western populations. About 15% of CRC patients report a family history of the disease. Studies on individuals with a genetic predisposition to CRC have been responsible for significant advances in the understanding of this disease. Thus, although developments in molecular biology have been mainly restricted to a minority of individuals with a hereditary background, information obtained from this group may affect the diagnosis and therapy of sporadic CRCs as well. Deficiency in the DNA ***mismatch***
repair (MMR) system results in microsatellite instability (MSI). Individuals from hereditary non-polyposis colorectal cancer (HNPCC) kindreds with ***germline*** mutations in genes involved in MMR may benefit from clinical screening programs. The higher frequency of MSI in HNPCC than in sporadic tumours suggests that involvement of MMR genes in sporadic adenomas may be uncommon. Consequently, MSI in adenomas could be a useful tool for HNPCC screening in the general population. Moreover, information gained from this subset of patients may aid in selecting appropriate endoscopic surveillance regimens, and in predicting the prognosis and response to treatment in patients with sporadic CRC exhibiting MSI. The purpose of this ***review*** is to discuss MSI and its clinical applications in colorectal malignancies, focusing on the HNPCC syndrome.

L19 ANSWER 4 OF 41 MEDLINE

ACCESSION NUMBER: 2001217833 MEDLINE

DOCUMENT NUMBER: 21206465 PubMed ID: 11309221

TITLE: Hereditary non-polyposis colorectal cancer (HNPCC): new
germline ***mutation*** (190-191 del AA) in the
human MLH1 gene and ***review*** of clinical guidelines
for surveillance of affected families.

AUTHOR: Schieman U; Papatheodorou L; Glasl S; Gross M

CORPORATE SOURCE: Medizinische Poliklinik, Ludwig-Maximilians-Universitat
Munchen, Pettenkoferstr. 8a, D-80336 Munchen, Germany..
uwe.schiemann@pk-i.med.uni-muenchen.de

SOURCE: EUROPEAN JOURNAL OF MEDICAL RESEARCH, (2001 Mar 26) 6 (3)
93-100.

Journal code: COQ; 9517857. ISSN: 0949-2321.

PUB. COUNTRY: Germany: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200106

ENTRY DATE: Entered STN: 20010611

09480389

Last Updated on STN: 20010611

Entered PubMed: 20010419

Entered Medline: 20010607

AB Hereditary non-polyposis colorectal cancer (HNPCC) is one of the most common genetic diseases comprising at least 5-6% of all colorectal cancers. It is characterized by early onset and mostly right-sided tumors (proximal to the splenic flexure). Molecular analyses are useful methods for diagnosis in index patients and for the detection of risk persons in affected families. A 37-year-old female patient whose family history fulfilled the criteria for hereditary non-polyposis colorectal cancer (HNPCC) was studied using PCR and DNA sequencing for the detection of mutations in the ***mismatch*** ***repair*** genes hMSH2 and hMLH1. Additionally, literature was reviewed (MEDLINE research until 2000) concerning clinical guidelines for surveillance in HNPCC families. A new deletion of two adenosine nucleotides (190-191 del AA) at codon 64 in exon 2 of the hMLH1 gene was found. The frameshift led to a stop codon at amino acid position 75. This ***mutation*** is considered to be disease causing in the development of the colorectal cancer of this family. Six publications with detailed recommendations for the surveillance of risk persons were found in the literature. Following their guidelines, colonoscopy is recommended from 20-30 years on for members of a family who fulfills either the Amsterdam criteria or the Bethesda criteria in combination with a detection of microsatellite instability. Female risk persons should be investigated gynecologically, including a transvaginal ultrasound examination, from 25-35 years on for the early detection of endometrial or ovarian cancer. Recommendations for gastroscopy, abdominal ultrasound examination and urine analysis are not given in all publications. Genetic counseling is recommended from 18 years on for all members of affected families.

L19 ANSWER 5 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001054786 EMBASE

TITLE: DNA repair mechanisms and gametogenesis.

AUTHOR: Baarends W.M.; van der Laan R.; Grootegeed J.A.

CORPORATE SOURCE: W.M. Baarends, Dept. of Endocrinology/Reproduction, Biology and Genetics, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, Netherlands. baarends@endov.fgg.eur.nl

SOURCE: Reproduction, (2001) 121/1 (31-39).

Refs: 66

ISSN: 1470-1626 CODEN: RCUKBS

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 002 Physiology
010 Obstetrics and Gynecology
021 Developmental Biology and Teratology
022 Human Genetics
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB In mammals, there is a complex and intriguing relationship between DNA repair and gametogenesis. DNA repair mechanisms are involved not only in the repair of different types of DNA damage in developing ***germline*** cells, but also take part in the meiotic recombination process. Furthermore, the DNA repair mechanisms should tolerate mutations occurring during gametogenesis, to a limited extent. In the present ***review***, several gametogenic aspects of DNA ***mismatch*** ***repair***, homologous recombination repair and postreplication repair are discussed. In addition, the role of DNA damage-induced cell cycle checkpoint control is considered briefly. It appears that many genes encoding proteins that

take part in DNA repair mechanisms show enhanced or specialized expression during mammalian gametogenesis, and several gene knockout mouse models show male or female infertility. On the basis of such knowledge and models, future experiments may provide more information about the precise relationship between DNA repair, chromatin dynamics, and genomic stability versus instability during gametogenesis.

L19 ANSWER 6 OF 41 MEDLINE

ACCESSION NUMBER: 2000412597 MEDLINE
 DOCUMENT NUMBER: 20413470 PubMed ID: 10956410
 TITLE: Distinct clinical features associated with microsatellite instability in colorectal cancers of young patients.
 AUTHOR: Ho J W; Yuen S T; Chung L P; Kwan K Y; Chan T L; Leung S Y; Chan A S; Tse C w; Lam P W; Luk I S
 CORPORATE SOURCE: Department of Surgery, University of Hong Kong Medical Centre, Queen Mary Hospital, Pokfulam, Hong Kong..
 JUDYHO@HKUCC.HKU.HK
 SOURCE: INTERNATIONAL JOURNAL OF CANCER, (2000 Jul 20) 89 (4) 356-60.
 Journal code: GQU; 0042124. ISSN: 0020-7136.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200008
 ENTRY DATE: Entered STN: 20000907
 Last Updated on STN: 20000907
 Entered Medline: 20000831

AB The Hong Kong Chinese population has an unusually high incidence of colorectal cancer in the young, suggestive of hereditary susceptibility. To search for a genetic basis for this predisposition, we studied the incidence of microsatellite instability (MSI) in paraffin-embedded colectomy specimens of 124 young (<50 years old) Chinese colorectal cancer patients referred to the Hong Kong Hereditary Gastrointestinal Cancer Registry from 1995 to 1998. By medical record ***review*** and personal interview, we searched for distinct clinical features associated with the manifestation of MSI in this group of patients. For patients with MSI tumours, blood was taken for detection of ***germline*** ***mutation*** in 2 ***mismatch*** ***repair*** (MMR) genes. MSI was present in 33 tumours from 23 males and 10 females (26.6%). Ongoing ***mutation*** analysis has so far identified MMR gene mutations in 8 patients with MSI tumours. The incidence of MSI increased significantly with decreasing age at cancer diagnosis. For patients aged 30 to 49, MSI tumours were located mainly at the proximal colon. However, for exceptionally young patients (<30 years), MSI tumours tended to be at the distal large bowel. This observation suggested a differential activity of the MMR pathway in colorectal carcinogenesis in different age groups. On multivariate analysis, young age at cancer diagnosis, proximal tumour location, a strong family history of colorectal cancer, and a personal history of metachronous cancer were independent predictors for MSI status. This knowledge may have an impact on the management of young colorectal cancer patients and their families.
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Ⓢ L19 ANSWER 7 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1999326059 EMBASE
 TITLE: A simple model of carcinogenesis of colorectal cancers with microsatellite instability.
 AUTHOR: Janin N.

09480389

CORPORATE SOURCE: N. Janin, 4, place du 11 Novembre, 92 240 Malakoff, France
SOURCE: Advances in Cancer Research, (2000) 77/- (189-221).

Refs: 83

ISSN: 0065-230X CODEN: ACRSAJ

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer

022 Human Genetics

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Lynch syndrome is a hereditary predisposition to colorectal cancer (CRC) and other cancers caused by ***germline*** mutations in ***mismatch*** ***repair*** (MMR) genes. Almost all the cancers diagnosed in Lynch syndrome have an acquired MMR deficiency, a replication error (RER) mutator phenotype that is also found in a minority of sporadic cancers developed in the target organs of Lynch syndrome. Lynch syndrome displays many curious features that cannot be accounted for by the prevailing concepts of carcinogenesis and genetics: (1) CRCs occur preferentially in the right side of the colon, whereas the majority of sporadic cases develop in the left colon; (2) the increased risk of CRC is not associated with an increased incidence of adenomatous polyps, which are necessary pre-cancerous lesions in the development of common CRCs; (3) the tumor spectrum in Lynch syndrome is restricted to the colon and some extracolonic sites, whereas the responsible MMR genes are ubiquitously expressed; (4) the tumor risk, which is negligible during childhood, becomes significant during adulthood at the age of 25 and thereafter remains essentially constant throughout the ages. (5) Finally, the sporadic counterparts to the CRCs diagnosed in the setting of Lynch syndrome very curiously develop almost exclusively in the right colon, whereas this right-sidedness is much less pronounced in Lynch syndrome. To explain these anomalies, we propose a model of RER+ carcinogenesis based on the simple idea that the RER mutator phenotype has only short-term viability in normal cells. The proposed model states that the RER+ carcinogenesis is divided into two clearly distinct evolutive phases: (1) a preliminary phase starting with the counter-selective loss of ***mismatch*** ***repair*** function, in which most clones with the RER mutator phenotype are eliminated through apoptosis or an accelerated aging process; (2) an explosive phase that is initiated only if mutations blocking apoptosis and senescence, rapidly acquired during the short life span of the nontransformed RER+ clones, eventually rescue one RER+ cell that gives rise to the malignant clone. It will be shown that this theoretical framework with its heterodox initiation process not only possesses the virtue of allowing an understanding of Lynch syndrome, but may also have broader applications to all research fields dealing with carcinogenesis.

L19 ANSWER 8 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000233872 EMBASE

TITLE: DNA ***mismatch*** ***repair*** genes and colorectal cancer.

AUTHOR: Wheeler J.M.D.; Bodmer W.F.; Wheeler J.M.D.; McC Mortensen N.J.

CORPORATE SOURCE: J.M.D. Wheeler, Cancer and Immunogenetics Laboratory, Institute of Molecular Medicine, John Radcliffe Hospital, Oxford OX3 9DS, United Kingdom

SOURCE: Gut, (2000) 47/1 (148-153).

Refs: 109

ISSN: 0017-5749 CODEN: GUTTAK

COUNTRY: United Kingdom

09480389

DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
022 Human Genetics
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Positional cloning and linkage analysis have shown that inactivation of one of the ***mismatch*** ***repair*** genes (hMLH1, hMSH2, hPMS1, hPMS2, GTBP/hMSH6) is responsible for the microsatellite instability or replication error (RER+) seen in more than 90% of hereditary nonpolyposis colorectal cancers (HNPCC) and 15% of sporadic RER+ colorectal cancers. In HNPCC, a ***germline*** ***mutation*** (usually in hMLH1 or hMSH2) is accompanied by one further event (usually allelic loss) to inactivate a ***mismatch*** ***repair*** gene. In contrast, somatic mutations in the ***mismatch*** ***repair*** genes are not frequently found in sporadic RER+ colorectal cancers. Hypermethylation of the hMLH1 promoter region has recently been described, and this epigenetic change is the predominant cause of inactivation of ***mismatch*** ***repair*** genes in sporadic RER+ colorectal and other cancers. Inactivation of a ***mismatch*** ***repair*** gene may occur early (before inactivation of the APC gene) and produce a raised ***mutation*** rate in a proportion of HNPCC patients, and these cancers will follow a different pathway to other RER+ cancers. However, it is likely that selection for escape from apoptosis is the most important feature in the evolution of an RER+ cancer.

• L19 ANSWER 9 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000059057 EMBASE

TITLE: The application of human complement factor H-related protein (BTA TRAK) in monitoring patients with bladder ***cancer***.

— AUTHOR: Malkowicz S.B.

CORPORATE SOURCE: Dr. S.B. Malkowicz, Division of Urology, Univ. of Pennsylvania Medical Center, 1 Rhoads Pavillion, 3400 Spruce Street, Philadelphia, PA 19104, United States

— SOURCE: Urologic Clinics of North America, (2000) 27/1 (63-73).
Refs: 40

ISSN: 0094-0143 CODEN: UCNADW

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
028 Urology and Nephrology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The BTA TRAK assay is a quantitative ***sandwich*** format enzyme ***immunoassay*** performed in a reference laboratory. It measures levels of human complement factor H-related protein (hCFHrp) which is similar to human complement factor H. Test characteristics reveal an overall sensitivity of 68% to 77.5% and a specificity of 50%-75%. Retrospective analysis of urine specimens employing hazard analysis suggests that BTA TRAK may have a role as a quantitative diagnostic marker in monitoring bladder ***cancer*** patients. Prospective studies are required to validate this application and other uses of the BTA TRAK assay in the management of bladder ***cancer*** patients.

L19 ANSWER 10 OF 41 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:547047 CAPLUS

09480389

DOCUMENT NUMBER: 134:27979
TITLE: Molecular genetics of hereditary nonpolyposis
colorectal cancer
AUTHOR(S): Boland, C. Richard
CORPORATE SOURCE: Department of Medicine and Cancer Center, University
of California, San Diego, CA, 92037, USA
SOURCE: Ann. N. Y. Acad. Sci. (2000), 910(Colorectal Cancer),
50-61
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A ***review*** , with 31 refs. The initial paradigm developed for
colorectal carcinogenesis was derived from the observation that these
tumors suffer a large no. of chromosomal losses. This phenomenon results
from unbalanced mitoses, and to date there is no clear explanation for
this type of genomic instability. In 1993, a second type of genomic
instability was detected and linked to 12-15% of sporadic tumors, as well
as 90% or more of the colon cancers in hereditary nonpolyposis colorectal
cancer (HNPCC). HNPCC tumors are typically diploid and do not have the
inactivating mutations at the tumor suppressor genes commonly found in the
other cancers. These tumors were found because they have a very large no.
(perhaps in excess of 105) of insertion or deletion mutations at
microsatellite sequences; as a result, this has been termed microsatellite
instability (MSI). The majority of HNPCC families can be linked to
germline mutations in the DNA ***mismatch*** ***repair***
(MMR) genes hMSH2 or hMLH1. ***Germline*** mutations in hMSH6 and
hPMS2 in HNPCC families are much less common. HNPCC tumors develop
through the accumulation of mutations at genes that control cellular
growth, and these genes are not the same as those recognized in the
initial pathway outlined by Vogelstein, B.; et al. (1988). The genetic
targets of MSI all contain repetitive sequences in coding regions that are
unstable when the DNA MMR system is inoperative. Certain pathol. features
have been identified that suggest that colon cancers have developed in the
setting of defective DNA MMR.

REFERENCE COUNT: 31
REFERENCE(S): (1) Aaltonen, L; Science 1993, V260, P812 CAPLUS
(3) Boland, C; Cancer Res 1998, V58, P5248 CAPLUS
(4) Boland, C; Nature Med 1995, V1, P902 CAPLUS
(6) Bronner, C; Nature 1994, V368, P258 CAPLUS
(7) Duval, A; Cancer Res 1999, V59, P4213 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 11 OF 41 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:225788 CAPLUS
DOCUMENT NUMBER: 133:15353
TITLE: Potential roles of genetic biomarkers in colorectal
cancer chemoprevention
AUTHOR(S): Syngal, Sapna; Clarke, Gerard; Bandipalliam, Prathap
CORPORATE SOURCE: Population Sciences Division, Dana-Farber Cancer
Institute and Harvard Medical School, Boston, MA, USA
SOURCE: J. Cell. Biochem. (2000), (Suppl. 34), 28-34
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A ***review*** with 38 refs. Colorectal cancer is a significant cause
of morbidity and mortality in industrialized societies and the second most
frequent cause of cancer death in the United States. Surrogate endpoint

biomarkers are gaining wide acceptance in early diagnosis and short-term cancer chemoprevention trials in place of cancer endpoints. Mol. genetic biomarkers can be useful tools in identifying subjects at risk of developing cancer and screening for early cancers amenable to complete cure. They may be useful both in predicting and assessing response to a given therapy and in detg. prognosis after an initial diagnosis has been made. Ideally, biomarkers should fulfill some, if not all, of the following criteria: variability of expression between phases of carcinogenesis, assocn. with cancer risk, ability to undergo modification in response to a chemopreventive agent, and finally, permit ease of measurement. In consideration of colorectal cancer chemoprevention, several genetic biomarkers seem to meet many of these criteria, as they do exhibit distinct variability of expression at different phases of carcinogenesis, are often strongly assocd. with increased cancer risk (esp. the hereditary/familial syndromes), are generally able to be measured relatively easily through peripheral blood sampling (

germline mutations) or by colonic mucosal sampling by endoscopic techniques (somatic mutations). In some cases, genetic biomarkers have also been demonstrated to undergo modification in response to a chemopreventive agent. With further understanding of the genetic and mol. changes involved in sporadic and familial colorectal carcinogenesis, genetic biomarkers appear to hold great potential for the identification of subjects at high risk of developing colorectal cancer, as well as the development of novel chemopreventive approaches and form a promising area for further research.

REFERENCE COUNT: 39

REFERENCE(S): (2) Bodmer, W; Nature 1987, V328, P614 CAPLUS
(8) Fearon, E; Cell 1990, V61, P759 CAPLUS
(16) Kelloff, G; Semin Oncol 1997, V24, P241 CAPLUS
(17) Kopreski, M; Br J Cancer 1997, V76, P1293 CAPLUS
(19) Laken, S; Nature Genet 1997, V17, P79 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 12 OF 41 MEDLINE

ACCESSION NUMBER: 2000013049 MEDLINE
DOCUMENT NUMBER: 20013049 PubMed ID: 10544223
TITLE: Genetic susceptibility to non-polyposis colorectal cancer.
AUTHOR: Lynch H T; de la Chapelle A
CORPORATE SOURCE: Department of Preventive Medicine and Public Health,
Creighton University School of Medicine, 2500 California
Plaza, Omaha, Nebraska 68178, USA.
CONTRACT NUMBER: ROICA 74684 (NCI)
SOURCE: JOURNAL OF MEDICAL GENETICS, (1999 Nov) 36 (11) 801-18.
Ref: 164
Journal code: J1F; 2985087R. ISSN: 0022-2593.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000124
Last Updated on STN: 20000124
Entered Medline: 20000113

AB Familial colorectal cancer (CRC) is a major public health problem by virtue of its relatively high frequency. Some 15-20% of all CRCs are familial. Among these, familial adenomatous polyposis (FAP), caused by ***germline*** mutations in the APC gene, accounts for less than 1%.

09480389

Hereditary non-polyposis colorectal cancer (HNPCC), also called Lynch syndrome, accounts for approximately 5-8% of all CRC patients. Among these, some 3% are ***mutation*** positive, that is, caused by ***germline*** mutations in the DNA ***mismatch*** ***repair*** genes that have so far been implicated (MLH1, MSH2, MSH6, PMS1, and PMS2). Most of the remaining patients belonging to HNPCC or HNPCC-like families are still molecularly unexplained. Among the remaining familial CRCs, a large proportion is probably caused by gene mutations and polymorphisms of low penetrance, of which the I1307K polymorphism in the APC gene is a prime example. Molecular genetic findings have enabled hereditary CRC to be divided into two groups: (1) tumours that show microsatellite instability (MSI), occur more frequently in the right colon, have diploid DNA, harbour characteristic mutations such as transforming growth factor beta type II receptor and BAX, and behave indolently, of which HNPCC is an example; and (2) tumours with chromosomal instability (CIN), which tend to be left sided, show aneuploid DNA, harbour characteristic mutations such as K-ras, APC, and p53, and behave aggressively, of which FAP is an example. This ***review*** focuses most heavily on the clinical features, pathology, molecular genetics, surveillance, and management including prophylactic surgery in HNPCC. Because of the difficulty in diagnosing HNPCC, a detailed differential diagnosis of the several hereditary CRC variants is provided. The extant genetic and phenotypic heterogeneity in CRC leads to the conclusion that it is no longer appropriate to discuss the genetics of CRC without defining the specific hereditary CRC syndrome of concern. Therefore, it is important to ascertain cancer of all anatomical sites, as well as non-cancer phenotypic stigmata (such as the perioral and mucosal pigmentations in Peutz-Jeghers syndrome), when taking a family cancer history.

L19 ANSWER 13 OF 41 MEDLINE

ACCESSION NUMBER: 2000157158 MEDLINE
DOCUMENT NUMBER: 20157158 PubMed ID: 10692769
TITLE: The role of the E-cadherin/catenin complex in gastrointestinal cancer.
AUTHOR: Debruyne P; Vermeulen S; Mareel M
CORPORATE SOURCE: Department of Radiotherapy and Nuclear Medicine, University Hospital Gent, Belgium.
SOURCE: ACTA GASTROENTEROLOGICA BELGICA, (1999 Oct-Dec) 62 (4) 393-402. Ref: 115
JOURNAL: Journal code: ONY; 0414075. ISSN: 0001-5644.
PUB. COUNTRY: Belgium
JOURNAL; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000407
Last Updated on STN: 20000407
Entered Medline: 20000328

AB Cancer is a genetic disease. The unstable genome of cancer cells causes tumour progression through multiple alterations in suppressor and promoter genes, leading to loss of homeostatic and gain of oncogenic functions. Invasion is the critical step in the acquisition of malignancy. It implicates a continuous molecular conversation of the cancer cells with other cells and with the extracellular matrix in which adhesion molecules are crucial. One of these, E-cadherin, is discussed in the present ***review***. E-cadherin is a transmembrane glycoprotein that forms a complex with cytoplasmic proteins, termed catenins because they link

E-cadherin to the actin cytoskeleton. E-cadherin/catenin-mediated intercellular adhesion and communication is mainly homophylic homotypic. There is compelling evidence from experiments in vitro as well as in vivo to accept that the E-cadherin/catenin complex acts as an invasion suppressor. The mechanism of this action is not only through cell-cell adhesion but also through transduction of signals to the cell's motility system. In the replication error positive human colon cancer cell line HCT-8, the alpha E-catenin gene CTNNB1 is an invasion suppressor gene. Here, the transition from the non-invasive to the invasive state was prevented by introduction into the unstable non-invasive cells of either an extra CTNNB1 or a wild type hMSH6 ***mismatch*** ***repair*** gene. beta-catenin also participates at a complex which comprises the adenomatous polyposis cancer protein APC. In colorectal cancer, ***mutation*** of either APC or beta-catenin is oncogenic.

Downregulation of the E-cadherin/catenin complex may occur in several ways amongst which are gene mutations, methylation of 5'CpG dinucleotides within the promotor region of E-cadherin, tyrosine phosphorylation of beta-catenin, cell surface expression of proteoglycans sterically hindering E-cadherin and proteolytic release of fragments from the extracellular part of E-cadherin. Upregulation of the E-cadherin/catenin complex has been realized with a series of agents, some of which can be used therapeutically. In most human gastrointestinal cancers the E-cadherin/catenin or related complexes are disturbed and this underscores their pivotal role in the progression of these tumours. Mutations of the E-cadherin gene, including ***germline*** mutations, occur in diffuse gastric carcinoma, CpG methylation around the promotor region of E-cadherin in hepatocellular carcinomas and mutations of the APC tumour suppressor gene or in the beta-catenin oncogene in most colorectal cancers. The literature agrees about the disturbance of immunohistochemical patterns of E-cadherin and catenin expression in gastrointestinal cancers. Conflicting opinions do, however, exist about the prognostic value of such immunohistochemical aberrations. We doubt that immunohistochemistry of E-cadherin or catenins add prognostic value to the already used histological grading systems. In our opinion the major benefit from understanding of the E-cadherin/catenin-mediated pathways of invasion will be the development of new anti-invasive treatment strategies.

L19 ANSWER 14 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1999095760 EMBASE

TITLE: Low hemoglobin is associated with increased serum levels of vascular endothelial growth factor (VEGF) in ***cancer*** patients. Does anemia stimulate angiogenesis?.

AUTHOR: Dunst J.; Pigorsch S.; Hansgen G.; Hintner I.; Lautenschlager C.; Becker A.

CORPORATE SOURCE: Dr. J. Dunst, Klin. für Strahlentherapie der Univ., Dryanderstrasse 4-7, D-06097 Halle, Germany. juergen.dunst@medizin.uni-halle.de

SOURCE: Strahlentherapie und Onkologie, (1999) 175/3 (93-96). Refs: 15

ISSN: 0179-7158 CODEN: STONE4

COUNTRY: Germany

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer

025 Hematology

LANGUAGE: English

SUMMARY LANGUAGE: English; German

AB Background: Vascular endothelial growth factor (VEGF) is an endothelial cell specific mitogen with strong angiogenic activity. Expression of VEGF

may therefore be an indicator for the angiogenic potential and biological aggressiveness of a tumor. Recently, measurement of the VEGF-protein in sera has become available. We report results of serum-VEGF in an unselected group of patients with ***cancer*** with special emphasis on a possible role of anemia. Patients and Methods: Between August 1997 and January 1998, serum-levels of VEGF were determined in a total number of 54 consecutive patients with previously untreated, non-metastatic carcinomas at the Department of Radiotherapy at the Martin-Luther-University Halle-Wittenberg. The age ranged from 35 through 89 years with a median age of 67 years. All patients had locoregional confined disease without evidence of hematogeneous metastases. Tumor sites were gynecological cancers in 22, head and neck in 14, gastrointestinal in 13, lung in 4 and prostate in 1 case. Forty-four patients had squamous carcinomas and 10 adenocarcinomas. Prior to treatment, routine laboratory work-up was done including measurement of serum-vascular endothelial growth factor (VEGF). The pretreatment hemoglobin ranged from 8.9 through 15.6 g/dl with a median of 13 g/dL VEGF was measured with a quantitative ***sandwich*** enzyme ***immunoassay*** technique. Results: The serum levels of VEGF in 40 patients with benign diseases ranged from 57 through 891 pg/ml with a mean of 267 .+- . 170 pg/ml. In the investigated 54 ***cancer*** patients, VEGF ranged from 62 through 2 609 pg/ml with a mean of 614 .+- . 551 pg/ml. Age, UICC/FIGO-stage, T- or N-category, primary tumor site, grade and histologic type had no significant impact on VEGF-serum levels. There was, however, an association between hemoglobin level and serum-VEGF with an increased mean serum-VEGF in 26 patients with a low hemoglobin (< 13 g/dl) as compared to 28 patients with a hemoglobin > 13 g/dl (805 .+- . 656 vs 438 .+- . 360, p = 0.016, 2- sided t-test). Conclusions: With regard to the recently established correlation between anemia and intratumoral hypoxia, the increased serum- VEGF levels in patients with low hemoglobin may be explained via hypoxia- induced VEGF secretion. This would suggest that anemia may stimulate angiogenesis via hypoxia. The hypothesis, however, requires further investigation and might have important therapeutical impact.

L19 ANSWER 15 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1999227709 EMBASE

TITLE: Molecular diagnostics of cancer predisposition: Hereditary non-polyposis colorectal carcinoma and ***mismatch*** ***repair*** defects.

AUTHOR: Bocker T.; Ruschoff J.; Fishel R.

CORPORATE SOURCE: R. Fishel, Kimmel Cancer Institute, Thomas Jefferson University, 233 South 10th St., Philadelphia, PA 19107, United States. rfishel@hendrix.jci.tju.edu

SOURCE: Biochimica et Biophysica Acta - Reviews on Cancer, (31 May 1999) 1423/3 (01-010).

Refs: 122

ISSN: 0304-419X CODEN: BBACEU

PUBLISHER IDENT.: S 0304-419X(99)00008-6

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
022 Human Genetics
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Hereditary non-polyposis colorectal carcinoma accounts for 5-13% of all colorectal carcinomas and is inherited in a dominant fashion. Two different forms can be distinguished. Type I is restricted to colorectal

cancers, whereas type II patients acquire colorectal, endometrial, gastric, small intestinal and transitional carcinomas of the upper urinary tract. ***Germline*** mutations in the human ***mismatch*** ***repair*** genes (hMSH2, hMSH6, hMLH1, hPMS2) account for the majority of hereditary non-polyposis colorectal carcinoma. As a result of the ***mismatch*** ***repair*** deficiency, replication errors are not repaired, resulting in a mutator phenotype. Simple repetitive sequences (microsatellites) are especially prone to replication errors and analysis of their stability combined with immunohistochemical analysis of ***mismatch*** ***repair*** protein expression provides a rapid diagnostic strategy. For patients either (1) fulfilling the Amsterdam criteria for HNPCC, (2) with synchronous or metachronous hereditary non-polyposis colorectal carcinoma-related tumors, (3) with hereditary nonpolyposis colorectal carcinoma-related tumors before the age of 45 and/or (4) with right sided CRC and mucinous, solid, or cribriform growth patterns, screening for ***mismatch*** ***repair*** deficiencies should be performed. The identification of colorectal cancers displaying a mutator phenotype has implications for both treatment and prognosis.

L19 ANSWER 16 OF 41 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:502815 CAPLUS
 DOCUMENT NUMBER: 129:134350
 TITLE: Hereditary nonpolyposis colorectal cancer
 AUTHOR(S): Yokozaki, Hiroshi; Tahara, Eiichi
 CORPORATE SOURCE: 1st Dep. Pathol., Hiroshima Univ., Hiroshima, 730, Japan
 SOURCE: Nippon Naika Gakkai Zasshi (1998), 87(7), 1382-1387
 CODEN: NNGAAS; ISSN: 0021-5384
 PUBLISHER: Nippon Naika Gakkai
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: Japanese
 AB A ***review*** with 10 refs., on identification of ***germline*** mutations in the DNA ***mismatch*** ***repair*** genes, including hMSH2 and hMLH1, assocd. with hereditary nonpolyposis colon cancer (HNPCC), and their possible application to genetic diagnosis. Databases on HNPCC are also introduced.

L19 ANSWER 17 OF 41 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:457494 CAPLUS
 DOCUMENT NUMBER: 129:159908
 TITLE: Hereditary non-polyposis colorectal cancer. MSH2, MLH1, PMS1, and PMS2 genes. Basic study
 AUTHOR(S): Yuasa, Yasuhito
 CORPORATE SOURCE: Fac. Med., Tokyo Med. Dent. Univ., Tokyo, 113, Japan
 SOURCE: Mol. Med. (Tokyo) (1998), 35(Suppl. 473), 276-279
 CODEN: MOLMEL; ISSN: 0918-6557
 PUBLISHER: Nakayama Shoten
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: Japanese
 AB A ***review*** with 5 refs. The function of ***mismatch*** ***repair*** (MMR) genes are described, and whose anomaly causes hereditary non-polyposis colorectal cancer (HNPCC). Most of ***germline*** mutations in HNPCC is in hMLH1 and hMSH2. The incidence of the anomaly in MMR in Japanese HNPCC families are by the order of hMSH2, hMLH1 and hMSH6. The ***mutation*** found in Japanese are listed. Gene diagnosis process is described. The process of tumorigenesis via adenoma generation is depicted from anomaly in MMR, in which lack of apoptosis occurs at the last step.

L19 ANSWER 18 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998276631 EMBASE
 TITLE: [Colorectal carcinoma as an example of molecular cancer predisposition diagnosis - What can pathology contribute?]. MOLEKULARE KREBSDISPOSITIONS-DIAGNOSTIK AM BEISPIEL DES KOLOREKTALEN KARZINOMS.
 AUTHOR: Ruschoff J.; Dietmaier W.; Bocker T.; Wallinger S.; Kullmann F.; Beham A.; Hofstadter F.
 CORPORATE SOURCE: Dr. J. Ruschoff, Institut für Pathologie, Stadtische Kliniken, Monchebergstrasse 41/43, D-34125 Kassel, Germany
 SOURCE: Pathologe, (1998) 19/4 (269-278).
 Refs: 52
 ISSN: 0172-8113 CODEN: PATHDE
 COUNTRY: Germany
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 005 General Pathology and Pathological Anatomy
 016 Cancer
 022 Human Genetics
 048 Gastroenterology
 LANGUAGE: German
 SUMMARY LANGUAGE: English; German

AB During the last few years, the molecular basis of several cancer predisposition syndromes has been discovered which offers new tools for cancer prevention and early detection. This will be demonstrated in one of the most frequent hereditary cancer syndromes, namely the hereditary nonpolyposis colorectal cancer (HNPCC) which accounts for about 5% to 8% of CRC. Thereby, families with exclusively CRC (Lynch type I syndrome) and those with extra-colonic cancers especially of endometrium, stomach, small bowel and upper urinary tract (Lynch type II syndrome) can be discriminated. At the molecular level, HNPCC is caused by ***germline*** mutations in one of the ***mismatch*** ***repair*** genes (hMSH2, hMLH1, hMSH6, hPMS2). Thus, nucleotide mispairings occurring particularly within simple repetitive genomic sequences (microsatellites) during replication are no longer be repaired properly and can be demonstrated by PCR as so-called microsatellite instability (MSI). Since more than 90% of HNPCC associated and only about 15% of sporadic CRC show MSI, this test is a useful tool for HNPCC screening. In case of a negative result HNPCC is highly unlikely. In positive cases (with .ltoreq.2 out of 5 unstable defined microsatellite markers) the definite molecular diagnosis can only be obtained by sequencing the ***mismatch*** ***repair*** genes from the patient's blood or normal DNA. As immunohistochemistry reveals loss of hMSH2 or hMLH1 expression in most MSI positive CRC, these data provide useful information for the sequencing strategy. Molecular tumor screening by MSI test and immunochemistry is recommended in patients i.) with a positive family history (acc. to the Amsterdam criteria), ii.) suffering from multiple HNPCC related carcinomas, iii.) with HNPCC related cancer before 45ys of age, and iv.) with right-sided CRC exhibiting medullary, signet-ring or mucinous differentiation. Finally, these tests as well as genetic counseling and treatment of the patient need to be done by an interdisciplinary approach. Thereby, the pathologist can substantially contribute to identify HNPCC related carcinomas either by clinical or morphological criteria and to initiate the molecular screening test.

6 L19 ANSWER 19 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998197733 EMBASE
 TITLE: Genetics and ovarian carcinoma.
 AUTHOR: Lynch H.T.; Casey M.J.; Lynch J.; White T.E.K.; Godwin A.K.
 CORPORATE SOURCE: Dr. A.K. Godwin, Department of Medical Oncology, Fox Chase

09480389

Cancer Center, 7701 Burholme Ave, Philadelphia, PA 19111,
United States

- SOURCE: Seminars in Oncology, (1998) 25/3 (265-280).

Refs: 132

ISSN: 0093-7754 CODEN: SOLGAV

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 010 Obstetrics and Gynecology

016 Cancer

017 Public Health, Social Medicine and Epidemiology

022 Human Genetics

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Ovarian cancer is a disease that will affect approximately 1% of American women during their lifetime, and contributes to more than 14,000 deaths annually. If not detected early, this disease has a 5-year survival rate of less than 20%. Ovarian cancer develops predominantly from the malignant transformation of a single cell type, the surface epithelium. Although the biological mechanisms of transformation remain unclear, it is probably a multistep process requiring an accumulation of genetic lesions in a number of different gene classes. Several proto-oncogenes, such as AKT2 and Ki-RAS, are activated during ovarian cancer development, with putative oncogene-containing chromosomal regions showing imbalances and DNA amplifications. A number of chromosomal regions are also lost in ovarian tumors, indicating that the inactivation of tumor suppressor genes, such as TP53, may also contribute to cancer development. An important recent advancement in the field of ovarian cancer research is the identification of the breast/ovarian cancer susceptibility genes, BRCA1 and BRCA2. Mutations in these two tumor suppressor genes are responsible for the majority of heritable forms of epithelial ovarian cancers. A second class of genes involved in DNA ***mismatch*** ***repair*** (MMR) are responsible for most cases of hereditary nonpolyposis colorectal cancer (HNPCC). HNPCC or Lynch II cancer syndrome patients are also at an increased risk for developing ovarian cancer. Individuals in cancer-prone kindreds are currently being screened for ***germline*** mutations in BRCA1, BRCA2, and several MMR genes (eg, MSH2, MLH1), and mutant allele carriers counseled for cancer risks. Issues related to counseling and management of women at high risk for developing ovarian cancer are discussed. Although BRCA1, BRCA2, and a number of MMR genes have been identified, many more genes involved in gynecologic malignancies remain to be discovered and the clinical significance of the cancer genes already known is still in its infancy.

L19 ANSWER 20 OF 41 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:727648 CAPLUS

DOCUMENT NUMBER: 128:45347

TITLE: Lectin/ ***antibody*** " ***sandwich*** "
ELISA for quantification of circulating mucin
as a diagnostic test for pancreatic ***cancer***

AUTHOR(S): Parker, Neil

CORPORATE SOURCE: Cortecs Diagnostics, Deeside Industrial Park, Deeside,
UK

SOURCE: Methods Mol. Med. (1998), 9(Lectin Methods and
Protocols), 249-253

CODEN: MMMEFN

PUBLISHER: Humana

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A discussion with 10 refs.

L19 ANSWER 21 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 1998106359 EMBASE
 TITLE: [Molecular genetics of colon cancer: Recent advances and clinical implications].
 MOLEKULARGENETIK DES KOLONKARZINOMS: AKTUELLE ASPEKTE UND KLINISCHE BEDEUTUNG.
 AUTHOR: Ebert M.; Rost H.; Malfertheiner P.
 CORPORATE SOURCE: Dr. M. Ebert, Klinik für Gastroenterologie, Hep-Itologie und Infektiologie, Otto-von Guericke Univ. Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany.
 Matthias.Ebert@Medizin.Uni-Magdeburg.de
 SOURCE: Leber Magen Darm, (1998) 28/2 (55-60).
 Refs: 51
 ISSN: 0300-8622 CODEN: LBMDAT
 COUNTRY: Germany
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 016 Cancer
 022 Human Genetics
 048 Gastroenterology
 LANGUAGE: German
 SUMMARY LANGUAGE: English; German

AB The pathogenesis of colorectal cancer has been the focus of recent molecular research. The adenoma-carcinoma sequence in colorectal cancer and its molecular alterations have been studied extensively and from the basis of multi-step-carcinogenesis. Furthermore, the identification of molecular alterations in hereditary colorectal cancer syndromes and sporadic colorectal cancer has changed the clinical management of these patients. ***Germline*** mutations of the APC gene are the basis for the development of familial adenomatous polyposis (FAP) and the detection of ***germline*** APC mutations in families with FAP determines their clinical follow-up. The presence of microsatellite instability has led to the detection of ***germline*** mutations of ***mismatch*** ***repair*** genes in hereditary nonpolyposis colorectal cancer. In sporadic colorectal cancer specific genetic alterations, such as APC, K-ras, p53-gene mutations, have been ascribed to specific histomorphological alterations, constituting the molecular basis of the 'adenoma-carcinoma- sequence'. In addition, mutations of ***mismatch*** ***repair*** genes have also been described in sporadic colorectal cancer. The 'de novo' carcinogenesis of colorectal cancer has been described recently and in a recent analysis adenomas have also been demonstrated to be of polyclonal origin. Thus, besides the 'traditional' concept of the adenoma-carcinoma-sequence, further models of colorectal carcinogenesis have to be taken into account.

L19 ANSWER 22 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 97206779 EMBASE
 DOCUMENT NUMBER: 1997206779
 TITLE: Brain tumor-polyposis syndrome: Two genetic diseases?.
 AUTHOR: Paraf F.; Jothy S.; Van Meir E.G.
 CORPORATE SOURCE: Dr. E.G. Van Meir, Lab. of Tumor Biology and Genetics, Service of Neurosurgery, CHUV BH 19-109, CH-1011 Lausanne, Switzerland. erwin.van-meir@chuv.hospvd.ch
 SOURCE: Journal of Clinical Oncology, (1997) 15/7 (2744-2758).
 Refs: 128
 ISSN: 0732-183X CODEN: JCONDN
 COUNTRY: United States
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 008 Neurology and Neurosurgery

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016 Cancer
022 Human Genetics
048 Gastroenterology

LANGUAGE: English
SUMMARY LANGUAGE: English

AB Purpose and Design: This report presents a comprehensive and statistical analysis of the brain tumor-polypsis (BTP) cases referred to as Turcot's syndrome in the literature. Results: BTP patients encompass a heterogeneous group that can be classified into two statistically distinct clinical entities based on phenotype of the polyps ($P = .0001$), presence of colorectal cancer ($P = .0001$), type of brain neoplasm, ie, glioma or medulloblastoma ($P = .0001$), presence of skin lesions ($P = .0004$) and cafeau-lait spots ($P = .0008$), as well as consanguinity ($P = .0135$). Conclusion: The first entity (BTP syndrome type 1) consists of patients who have glioma and colorectal adenomas without polyposis (non-FAP cases), and their siblings with glioma and/or colorectal adenomas. For these patients, we show that the patient's age at malignant glioma occurrence is less than 20 years (50 to 80 years in the general population), which strongly supports the existence of an underlying genetic cause. The neoplasms of these patients show DNA replication errors, which suggests a relationship with hereditary nonpolyposis colorectal cancer (HNPCC), a disease characterized by ***germline*** alterations in DNA ***mismatch*** ***repair*** genes. The second entity (BTP syndrome type 2) consists of patients with a CNS tumor that occurs in a familial adenomatous polyposis kindred (FAP cases). These patients carry ***germline*** mutations in the APC gene, which suggests that mutations in this gene might predispose to brain tumors. Risk analysis shows increased incidence of medulloblastoma in FAP patients, but APC mutations are not found in sporadic glioma or medulloblastoma. Therefore, further investigations should establish whether the occurrence of medulloblastoma in an FAP family represents a variant of FAP.

L19 ANSWER 23 OF 41 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:563599 CAPLUS

DOCUMENT NUMBER: 127:218600

TITLE: DNA ***mismatch*** ***repair*** gene mutations
in human cancer

AUTHOR(S): Peltomaki, Paivi

CORPORATE SOURCE: Department of Medical Genetics, University of
Helsinki, Helsinki, FIN-00014, Finland

SOURCE: Environ. Health Perspect. Suppl. (1997), 105(4),
775-780

CODEN: EHPSEO; ISSN: 1078-0475

PUBLISHER: National Institute of Environmental Health Sciences

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A ***review*** with 81 refs. A new pathogenetic mechanism leading to cancer has been delineated in the past 3 yr when human homologs of DNA ***mismatch*** ***repair*** (MMR) genes have been identified and shown to be involved in various types of cancer. ***Germline*** mutations of MMR genes cause susceptibility to a hereditary form of colon cancer, hereditary nonpolyposis colon cancer (HNPCC), which represents one of the most common syndromes assocd. with cancer predisposition in man. Tumors from HNPCC patients are hypermutable and show length variation at short tandem repeat sequences, a phenomenon referred to as microsatellite instability or replication errors. A similar abnormality is found in a proportion of sporadic tumors of the colorectum as well as a variety of other organs; acquired mutations in MMR genes or other endogenous or exogenous causes may underlie these cases. Genetic and biochem.

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characterization of the functions of normal and mutated MMR genes elucidates mechanisms of cancer development and provides tools for diagnostic applications.

L19 ANSWER 24 OF 41 MEDLINE

ACCESSION NUMBER: 97284894 MEDLINE
DOCUMENT NUMBER: 97284894 PubMed ID: 9140167
TITLE: Familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC): a ***review*** of clinical, genetic and therapeutic aspects.
AUTHOR: Soravia C; Bapat B; Cohen Z
CORPORATE SOURCE: Department of Surgery, Mount Sinai Hospital, Toronto, Canada.. soravia@mshri.on.ca
SOURCE: SCHWEIZERISCHE MEDIZINISCHE WOCHENSCHRIFT. JOURNAL SUISSE DE MEDECINE, (1997 Apr 19) 127 (16) 682-90. Ref: 118
Journal code: UEI; 0404401. ISSN: 0036-7672.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970709
Last Updated on STN: 19970709
Entered Medline: 19970623

AB Familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) are two syndromes of colorectal cancer predisposition, inherited in an autosomal dominant fashion. They account for about 1% and 5-7% of all colorectal cancer cases, respectively. FAP is caused by ***germline*** mutations of a tumour suppressor gene, the adenomatous polyposis coli (APC) gene, whereas HNPCC results from genetic alterations of the DNA ***mismatch*** ***repair*** genes. Clinical manifestations in FAP include colonic as well as extracolonic sites (duodenum, eye, dental, nervous or connective tissues). In FAP, prophylactic colectomy is required in all affected patients and regular endoscopic check-up of the upper gastrointestinal tract is necessary to detect malignant transformation of duodenal polyps; medical management of complex desmoid tumours is preferred rather than surgery. In HNPCC, there are extracolonic associated endometrial, gastric, small bowel or brain carcinomas. At present time, for HNPCC patients, only preventive measures such as regular colonoscopic or gynecologic examinations are recommended, since prophylactic colectomy or hysterectomy are not considered to be routine procedures.

L19 ANSWER 25 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 97140096 EMBASE
DOCUMENT NUMBER: 1997140096
TITLE: The natural somatic ***mutation*** frequency and human carcinogenesis.
AUTHOR: Simpson A.J.G.
CORPORATE SOURCE: A.J.G. Simpson, Laboratory of Cancer Genetics, Ludwig Institute for Cancer Research, Sao Paulo, SP 01509-010, Brazil
SOURCE: Advances in Cancer Research, (1997) 71/- (209-240).
Refs: 139
ISSN: 0065-230X CODEN: ACRSAJ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer
 022 Human Genetics
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB Much recent attention has been paid to the important role of the DNA
 mismatch ***repair*** system in controlling the accumulation
 of somatic mutations in human tissues and the association of
 mismatch ***repair*** deficiency with carcinogenesis. In the
 absence of an intact ***mismatch*** ***repair*** system, cells
 accumulate mutations at a rate some 1000 times faster than normal cells,
 and this mutator phenotype is easily measured by the detection of the
 formation of new variant alleles at microsatellite loci. However, the
 mismatch ***repair*** system is not 100% efficient, even when
 intact, and the pattern of microsatellite alterations in a wide variety of
 tumors is consistent with these being due to clonal amplification from
 tissues that are genetically heterogeneous at microsatellite loci rather
 than ***mismatch*** ***repair*** deficiency in the tumor itself.
 On this basis, it can be estimated that the ***mutation*** frequency
 of microsatellites in normal human tissues is approximately 10-2 per locus
 per cell. Similarly, a frequency of ***mutation*** at minisatellite
 loci in normal tissues of around 10-1 per locus per cell can be estimated.
 Such elevated levels of ***mutation*** are consistent with a recent
 study of the frequency of HPRT ***mutation*** in human kidneys that
 demonstrated these to be frequent (average 2.5×10^{-4} in individuals of 70
 years or more) and exponentially related to age. Taken as a whole, the
 data suggest that somatic ***mutation*** in human epithelial cells may
 be some 10-fold higher than in peripheral blood lymphocytes and that the
 underlying rate of spontaneous ***mutation*** is sufficient to account
 for a large proportion of human carcinogenesis without the need to evoke
 either stepwise alteration to a mutator phenotype or clonal expansion at
 all the ***mutation*** steps in carcinogenesis. The exponential
 increase in ***mutation*** frequency with age is predictable on the
 basis that the ***mutation*** rate is controlled at the level of
 repair and that ***mutation*** in genes that affect the efficiency of
 these processes will gradually increase the underlying rate. In addition,
 the age relatedness of ***mutation*** frequency strongly supports the
 concept that ***mutation*** is cell division dependent and that
 cellular proliferation per se is an important risk factor for cancer.
 Comparison of somatic mutations with those in the human ***germline***
 mutation suggests common mechanistic origins and that the high
 levels of somatic ***mutation*** that occur are a direct reflection of
 the ***germline*** ***mutation*** rate selected over evolutionary
 time. Thus, the somatic accumulation of mutations can be seen as a natural
 process within the human body and cancer a normal part of the human life
 cycle. This point of view may explain why it has been so difficult to
 significantly reduce cancer incidence and suggests that, for this to be
 achieved, the means of altering the natural somatic ***mutation***
 rate needs to be identified.

L19 ANSWER 26 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 97069055 EMBASE
 DOCUMENT NUMBER: 1997069055
 TITLE: Hereditary ovarian cancer: Molecular genetics and clinical
 implications.
 AUTHOR: Boyd J.; Rubin S.C.
 CORPORATE SOURCE: J. Boyd, Division of Gynecologic Oncology, Department of
 Obstetrics/Gynecology, Pennsylvania University Medical
 Ctr., Philadelphia, PA 19104, United States
 SOURCE: Gynecologic Oncology, (1997) 64/2 (196-206).

Refs: 152
ISSN: 0090-8258 CODEN: GYNOA3

COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 010 Obstetrics and Gynecology
016 Cancer

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Epidemiologic data support the existence of two discrete manifestations of hereditary ovarian carcinoma: the breast and ovarian cancer syndrome and the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome. Genetic linkage analyses reveal that the majority of breast and ovarian cancer families are linked to the BRCA1 gene, while some cases of hereditary ovarian cancer are also apparent in breast cancer families linked to the BRCA2 gene. The majority of HNPCC families are linked to one of four genes encoding a family of DNA ***mismatch*** ***repair*** proteins. Molecular analyses demonstrate that genetic screening for ***germline*** transmission of a defective allele of one or another of these genes is now possible for high-risk individuals. The ethical, legal, and social implications of this type of analysis are multiple and complex, and genetic counseling requires a thorough understanding of these issues and a cautious approach to most effectively meet the special needs of this patient population. Increased medical surveillance and prophylactic oophorectomy are among the management options that may be appropriate for some genetically predisposed, asymptomatic women. Further research is needed regarding the most effective use of this genetic information in formulating counseling and clinical management strategies.

L19 ANSWER 27 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 97140093 EMBASE

DOCUMENT NUMBER: 1997140093

TITLE: Mutations predisposing to hereditary nonpolyposis colorectal cancer.

AUTHOR: Peltomaki P.; De la Chapelle A.

CORPORATE SOURCE: P. Peltomaki, Department of Medical Genetics, Haartman Institute, University of Helsinki, 00290 Helsinki, Finland

SOURCE: Advances in Cancer Research, (1997) 71/- (93-119).

Refs: 117

ISSN: 0065-230X CODEN: ACRSAJ

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer
022 Human Genetics
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Since 1993 four genes have been identified that, when mutated, confer predisposition to a form of hereditary colon cancer (hereditary nonpolyposis colorectal cancer [HNPCC]). These genes belong to the Mut-related family of DNA ***mismatch*** ***repair*** genes whose protein products are responsible for the recognition and correction of errors that arise during DNA replication. Mutational inactivation of both copies of a DNA ***mismatch*** ***repair*** gene results in a profound repair defect demonstrable by biochemical assays, and in vivo this defect is presumed to lead to progressive accumulation of secondary mutations throughout the genome, some of which affect important growth-regulatory genes and, hence, give rise to cancer. To date, more than 70 different ***germline*** mutations have been detected in DNA ***mismatch*** ***repair*** genes and shown to be associated with

SUMMARY LANGUAGE: English

AB A genome-wide instability has been found in almost all analyzed malignant tumors from patients with hereditary non-polyposis colorectal cancer (HNPCC), and in a subgroup of sporadic (non-inherited) cancers of the same type. This mutator phenotype was initially seen as novel alleles at microsatellite loci (a family of repetitive DNA sequences) and was shown to be caused by mutations in the highly conserved ***mismatch*** ***repair*** genes. Mutations have been found in each of four of these human genes: hMSH2, hMLH1, hPMS1 and hPMS2, in the ***germline*** of HNPCC patients and in their tumors, as well as in sporadic tumors. These recent discoveries provide new molecular diagnostic tools for the detection of patients at high risk of developing carcinomas of the large bowel and other HNPCC-related tumors. Ongoing international research is progressively solving many of the unanswered questions at the genotypic and phenotypic levels of this newly identified mechanism in carcinogenesis.

L19 ANSWER 30 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 97324903 EMBASE

DOCUMENT NUMBER: 1997324903

TITLE: Hereditary ovarian cancer: Genetic basis and management issues.

AUTHOR: Friedlander M.; Tucker K.

CORPORATE SOURCE: M. Friedlander, Department of Medical Oncology, Hereditary Cancer Clinic, Prince of Wales Hospital, Randwick, NSW, Australia

SOURCE: Cancer Forum, (1997) 21/1 (10-13).

Refs: 32

ISSN: 0311-306X CODEN: CAFODQ

COUNTRY: Australia

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 010 Obstetrics and Gynecology

016 Cancer

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Understanding of the molecular genetic basis for hereditary ovarian cancer has increased dramatically and a number of genes including BRCA1, BRCA2 and ***mismatch*** ***repair*** genes are now known to be associated with inherited susceptibility to ovarian cancer. The risk of ovarian cancer associated with ***germline*** mutations of these genes and the management options for women with a family history of ovarian cancer are reviewed.

L19 ANSWER 31 OF 41 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1996:558684 CAPLUS

DOCUMENT NUMBER: 125:192141

TITLE: ***Mismatch*** ***repair*** defects in human carcinogenesis

AUTHOR(S): Eshleman, James R.; Markowitz, Sandord D.

CORPORATE SOURCE: Dep. Pathology, Med., Ireland Cancer Center, Univ. Hosp. Cleveland, Case Western Reserve Univ., Cleveland, OH, 44106, USA

SOURCE: Hum. Mol. Genet. (1996), 5(Riv. Issue), 1489-1494

CODEN: HMGEE5; ISSN: 0964-6906

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A ***review*** with 81 refs. ***Mismatch*** ***repair*** defects are carcinogenic. This conclusion comes some 80 yr after the original description of a type of familial colorectal cancer in which

mismatch ***repair*** defects are involved, and from decades of dedicated basic science research into fundamental mechanisms cells use to repair their DNA. ***Mismatch*** ***repair*** (MMR) was described first in bacteria, later in yeast and finally in higher eukaryotes. In bacteria, one of its roles is the rapid repair of replicative errors thereby providing the genome with a 100-1000-fold level of protein against ***mutation*** . It also guards the genome by preventing recombination between non-homologous regions of DNA. The information gained from bacteria suddenly became relevant to human neoplasia in 1993 when the RER phenotype of microsatellite instability was discovered in human cancers and was rapidly shown to be due to defects in ***mismatch*** ***repair*** . Evidence supporting the role of MMR defects in carcinogenesis comes from a variety of independent sources including: (i) theor. considerations of the requirement for a mutator phenotype as a step in multistage carcinogenesis, (ii) discovering that MMR defects cause a 'mutator phenotype' destabilizing endogenous expressed genes including those integral to carcinogenesis; (iii) finding MMR defects in the ***germline*** of HNPCC kindred members; (iv) finding that such defects behave as classic tumor suppressor genes in both familial and sporadic colorectal cancers; (v) discovering that MMR 'knockout' mice have an increased incidence of tumors; and (vi) discovering that genetic complementation of MMR defective cells stabilizes the MMR deficiency-assocd. microsatellite instability. Models of carcinogenesis now must integrate the concepts of a MMR defect induced mutator phenotype (Loeb) with the concepts of multistep colon carcinogenesis (Fearon and Vogelstein) and clonal heterogeneity/selection (Nowell).

L19 ANSWER 32 OF 41 MEDLINE

ACCESSION NUMBER: 96424413 MEDLINE
 DOCUMENT NUMBER: 96424413 PubMed ID: 8826936
 TITLE: Hereditary nonpolyposis colorectal cancer (Lynch syndrome).
 An updated ***review***
 AUTHOR: Lynch H T; Smyrk T
 CORPORATE SOURCE: Department of Preventive Medicine, Creighton University
 School of Medicine, Omaha, Nebraska, USA.
 SOURCE: CANCER, (1996 Sep 15) 78 (6) 1149-67. Ref: 125
 Journal code: CLZ; 0374236. ISSN: 0008-543X.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
 ENTRY MONTH: 199611
 ENTRY DATE: Entered STN: 19961219
 Last Updated on STN: 19961219
 Entered Medline: 19961105

AB BACKGROUND: Hereditary nonpolyposis colorectal cancer (HNPCC) dates to Aldred Warthin's description of Family G a century ago. The phenotype features an excess of early onset colorectal carcinoma (CRC) with a propensity to involve the proximal colon, and a variety of extracolonic cancers, particularly carcinoma of the endometrium, ovary, stomach, small bowel, ureter, and renal pelvis. The recent discovery that HNPCC patients carry ***germline*** mutations in DNA ***mismatch*** ***repair*** genes has engendered great interest in the syndrome. METHODS: This is a description of HNPCC based on the authors' experience with more than 170 families and a ***review*** of the world literature. RESULTS: This ***review*** describes the genotypic and

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phenotypic features of HNPCC. The distinctive natural history of the syndrome is discussed in light of the recent discovery that ineffective DNA ***mismatch*** ***repair*** is the principal abnormality in affected individuals. CONCLUSIONS: Clinical and molecular genetic knowledge about HNPCC is now available to physicians, and should enable them to provide highly targeted surveillance and management for patients with a high cancer risk. Genetic counseling can prove lifesaving. The study of HNPCC will likely contribute to knowledge about the causes and control of common forms of cancer in the general population.

L19 ANSWER 33 OF 41 MEDLINE

ACCESSION NUMBER: 96298339 MEDLINE
DOCUMENT NUMBER: 96298339 PubMed ID: 8723065
TITLE: Hereditary nonpolyposis colorectal cancer: ***review***
of clinical, molecular genetics, and counseling aspects.
AUTHOR: Bellacosa A; Genuardi M; Anti M; Viel A; Ponz de Leon M
CORPORATE SOURCE: Istituti di Genetica Medica, Facolta di Medicina e
Chirurgia A. Gemelli, Universita Cattolica S. Cuore, Roma,
Italy.
SOURCE: AMERICAN JOURNAL OF MEDICAL GENETICS, (1996 Apr 24) 62 (4)
353-64. Ref: 115
Journal code: 3L4; 7708900. ISSN: 0148-7299.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961015
Last Updated on STN: 19961015
Entered Medline: 19961003

AB Lynch syndrome, or hereditary nonpolyposis colon cancer (HNPCC), is an autosomal-dominant disease accounting for approximately 1-5% of all colorectal cancer cases. Due to the lack of pathognomonic morphological or biomolecular markers, HNPCC has traditionally posed unique problems to clinicians and geneticists alike, both in terms of diagnosis and clinical management. Recently, novel insight into the pathogenesis of this syndrome has been provided by the identification of its molecular basis. In HNPCC families, ***germline*** mutations in any of four genes encoding proteins of a specialized DNA repair system, the ***mismatch*** ***repair***, predispose to cancer development. Mutations in ***mismatch*** ***repair*** genes lead to an overall increase of the ***mutation*** rate and are associated with a phenotype of length instability of microsatellite loci. The present report summarizes the clinicopathological aspects of HNPCC and reviews the most recent molecular and biochemical findings.

L19 ANSWER 34 OF 41 MEDLINE

ACCESSION NUMBER: 96283821 MEDLINE
DOCUMENT NUMBER: 96283821 PubMed ID: 8681938
TITLE: DNA-replication fidelity, ***mismatch*** ***repair***
and genome instability in cancer cells.
AUTHOR: Umar A; Kunkel T A
CORPORATE SOURCE: Laboratory of Molecular Genetics, National Institute of
Environmental Health Sciences, North Carolina 27709, USA.
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1996 Jun 1) 238 (2)
297-307. Ref: 81
Journal code: EMZ; 0107600. ISSN: 0014-2956.

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PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960828
Last Updated on STN: 19980206
Entered Medline: 19960822

AB It has been suggested that an early event in the multistep progression of a normal cell to a tumor cell could be a defect that leads to an elevated ***mutation*** rate, thus providing a pool of mutants upon which selection could act to yield a tumor. Such a mutator phenotype could result from a defect in any of several DNA transactions, including those that determine the DNA replication error rate or the ability to correct replication errors. Recent evidence for the latter is the mutator phenotype observed in tumor cells of patients having a hereditary form of colon cancer. These patients have a ***germline*** ***mutation*** in genes required for post-replication DNA ***mismatch*** ***repair***. A second ***mutation*** arises somatically, yielding a greatly elevated ***mutation*** rate due to an inability to correct DNA replication errors. This connection between cancer, DNA replication errors and defective ***mismatch*** ***repair*** is the subject of this ***review***, wherein we consider the key steps and principles for high fidelity replication and how their perturbation results in genome instability.

L19 ANSWER 35 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 96317935 EMBASE
DOCUMENT NUMBER: 1996317935
TITLE: Molecular genetics of polyposis and hereditary colorectal cancer.
AUTHOR: Radice P.; Cama A.; Mariani-Costantini R.
CORPORATE SOURCE: Divisione Oncologia Sperimentale A, Ist Nazionale Studio Cura dei Tumori, Via Venezian 1, 20133 Milano, Italy
SOURCE: FORUM - Trends in Experimental and Clinical Medicine, (1996) 6/3 (275-291).
ISSN: 1121-8142 CODEN: FTCME2
COUNTRY: Italy
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
022 Human Genetics
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Although the genetics of an inherited predisposition to colorectal carcinomas are still far from being completely elucidated, significant acquisitions have been achieved in the last few years. In fact, the genetic determinants of two major syndromes associated with susceptibility to colorectal cancer, familial adenomatous polyposis (FAP) and hereditary non polyposis colorectal cancer (HNPCC) have been identified. FAP appears to be a monogenic disease, due to mutations in the APC gene. This gene encodes a large protein, that appears to be involved in the control of signal transmission from the extracellular environment to the cytoskeleton and vice versa. Most APC gene mutations result in truncated APC proteins. The site of the ***germline*** APC mutations correlates with phenotypic manifestations of the disease. A number of studies demonstrated that in accordance with Knudson's hypothesis, biallelic inactivation of

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the APC gene occurs in both colorectal and extracolorectal tumours associated with FAP. In contrast with FAP, HNPCC is characterised by a high degree of genetic heterogeneity and four different genes, namely hMSH2, hMLH1, hPMS1 and hPMS2 which have mutated in affected individuals. These genes, termed DNA ***mismatch*** ***repair*** (MMR) genes, are the human counterparts of loci that in lower organisms control the fidelity of DNA replication. The discovery of human MMR genes has led to the identification of a new mechanism of carcinogenesis based on the acquisition by the cell of a so called 'mutator phenotype'.

L19 ANSWER 36 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 97128140 EMBASE

DOCUMENT NUMBER: 1997128140

TITLE: Manipulation of the mouse ***germline*** in the study of Min-induced neoplasia.

AUTHOR: Bilger A.; Shoemaker A.R.; Gould K.A.; Dove W.F.

CORPORATE SOURCE: A. Bilger, McArdle Laboratory Cancer Research, University Wisconsin Medical School, Madison, WI 53706, United States
Seminars in Cancer Biology, (1996) 7/5 (249-260).

SOURCE: Refs: 118

ISSN: 1044-579X CODEN: SECBE7

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer
022 Human Genetics
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The Min mouse, generated by random ***germline*** mutagenesis, carries a ***mutation*** in the mouse homolog of APC and is a model of inherited human intestinal tumorigenesis. To identify other genes in the pathway(s) of intestinal tumorigenesis genes that modify the Min phenotype have been sought. Several have been identified, including Mom1 and the genes for the 5-cytosine DNA methyltransferase and the DNA ***mismatch*** ***repair*** factor Msh2. Min-dependent tumorigenesis also occurs in mammary glands, the pancreas, and the body wall. The Min mouse has therefore become a model for tumorigenesis in a variety of organs. Identifying modifiers of its phenotype will help in piecing together the pathways of tumorigenesis in each of these tissues.

L19 ANSWER 37 OF 41 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1996:101370 CAPLUS

DOCUMENT NUMBER: 124:142234

TITLE: Mutator genes and mosaicism in colorectal cancer

AUTHOR(S): Dunlop, Malcolm G.

CORPORATE SOURCE: Dep. Surgery, Univ. Edinburgh, Edinburgh, EH4 2XU, UK
SOURCE: Curr. Opin. Genet. Dev. (1996), 6(1), 76-81

CODEN: COGDET; ISSN: 0959-437X

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A ***review*** with 55 refs. Recent studies have shed light on the role of defective DNA ***mismatch*** ***repair*** in human cancer. An elevated ***mutation*** rate assocd. with ***mismatch*** ***repair*** deficiency has been demonstrated in the ***germline*** and normal tissue from patients with hereditary non-polyposis colorectal cancer and transgenic animals resp. Thus ***mismatch*** ***repair*** deficiency may permit the accumulation of mutations in cancer genes that do not confer growth advantage. This represents one potential mechanism for the induction of mutational mosaicism in humans.

L19 ANSWER 38 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 95230501 EMBASE
 DOCUMENT NUMBER: 1995230501
 TITLE: Hereditary nonpolyposis colorectal cancer: The syndrome, the genes, and historical perspectives.
 AUTHOR: Marra G.; Boland C.R.
 CORPORATE SOURCE: Division of Gastroenterology, Department of Internal Medicine, Univ. of Michigan Medical Center, 200 Zina Pitcher Pl., Ann Arbor, MI 48109-0586, United States
 SOURCE: Journal of the National Cancer Institute, (1995) 87/15 (1114-1125).
 ISSN: 0027-8874 CODEN: JNCIAM
 COUNTRY: United States
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 016 Cancer
 022 Human Genetics
 048 Gastroenterology
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB Hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant disorder characterized by the occurrence within a family of multiple cases of colorectal cancer in the absence of gastrointestinal polyposis. The prevalence of this syndrome is not yet clear, but it may account for 1%5% of all colorectal cancers. Prior to the identification of the genetic basis of this syndrome, the disease was recognized by the familial aggregation of colorectal cancers that had an early age of onset, an excess of proximally located, and often multiple, primary tumors, and an excess occurrence of cancers in certain other organs. The recent description of an abnormality called 'microsatellite instability,' present in almost all cancers from HNPCC patients and in about 12%15% of sporadic cases, led to a series of discoveries that linked this type of genomic instability to a defect in the DNA ***mismatch*** ***repair*** (MMR) system. Independent investigators have identified four HNPCC genes: hMSH2 (a homologue of the prokaryotic DNA MMR gene MutS) and hMLH1, hPMS1, and hPMS2 (all homologues of the prokaryotic DNA MMR gene MutL). Mutations in each of the four genes have been found in the ***germline*** cells of HNPCC families. A major target for research in this area is the development of clinically practical screening tests for the genetic carrier state of HNPCC.

L19 ANSWER 39 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 96002375 EMBASE
 DOCUMENT NUMBER: 1996002375
 TITLE: Genetics of hereditary colon cancer.
 AUTHOR: De la Chapelle A.; Peltomaki P.
 CORPORATE SOURCE: Department of Medical Genetics, Folkhalsan Institute of Genetics, University of Helsinki, 00290 Helsinki, Finland
 SOURCE: Annual Review of Genetics, (1995) 29/- (329-348).
 ISSN: 0066-4197 CODEN: ARVGB7
 COUNTRY: United States
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 016 Cancer
 022 Human Genetics
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB A new mechanism leading to cancer has been delineated in the last two years when genes whose mutations cause susceptibility to hereditary nonpolyposis colorectal cancer, HNPCC, have been mapped, cloned, and

characterized. The genes involved belong to a family of DNA

mismatch ***repair*** genes, and the homozygous effects of their mutations lead to a so-called mutator or replication error phenotype characterized by genome-wide mutations most readily detectable as lengthening or shortening of microsatellite repeats in tumor tissue as compared to normal tissue from the same individual. ***Germline*** mutations are inherited in a dominant Mendelian fashion causing the multiorgan cancer susceptibility syndrome misnamed HNPCC. Clinically, the molecular characterization of these mutations in affected individuals now allows genotype-phenotype correlations, and a new view of the natural history of the disease may arise. In at risk individuals, it allows predictive testing for cancer susceptibility, enhanced clinical surveillance with the aim of early cancer detection and cure, and preventive measures.

L19 ANSWER 40 OF 41 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1994:505380 CAPLUS

DOCUMENT NUMBER: 121:105380

TITLE: Membrane glycoproteins and oncogenes as markers in breast ***cancer***

AUTHOR(S): Ohuchi, Noriaki; Taeda, Yoshinori; Yaegashi, Sadanori; Harada, Yuko; Kanda, Teru; Mori, Shozo

CORPORATE SOURCE: Department Surgery, Tohoku University School Medicine, Sendai, 980, Japan

SOURCE: Cancer Mol. Biol. (1994), 1(3), 179-92

CODEN: ICMBEZ

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A ***review*** and discussion with 104 refs. on cell surface antigens recognized by monoclonal antibodies (MAbs) and altered glycosylation of membrane glycoproteins assocd. with breast ***cancer***. MUC1, TAG-72 and CEA have been recognized as breast ***cancer*** -assocd. antigens and the clin. application of MAbs recognizing the distinctive antigens are utilized in the management of breast ***cancer*** patients. A new tumor-assocd. antigen, designated AM antigen defined by MAb AM-1, was characterized. AM-1, generated against HMA-1 human breast ***cancer*** cell line, showed a preferential reactivity to breast ***cancer*** cells vs. to normal or benign epithelial cells. AM-1 recognized high mol. wt. components of 160-210 kDa and > 370 kDa. Enzyme digestion of pptd. antigens demonstrated that AM antigen contains O-linked and N-linked carbohydrates with neuraminic acid structures. Binding inhibition and ***sandwich*** ***ELISA*** assays using MAbs reactive with known breast ***cancer*** -assocd. antigens and synthetic MUC1 core peptide demonstrated that AM antigen is distinct from CEA, TAG-72 or MUC1 antigens, while it conjoins with MUC1 and TAG-72 as a trimer form, suggesting that MAb AM-1 recognizes a novel glycoprotein which may be utilized in the management of breast ***cancer***. The .beta.1-6 branched oligosaccharide is expressed in human colon, breast and esophageal cancers. Two L-PHA-reactive sialylated glycoproteins, 170 and 120 kDa, have been detected in breast ***cancer*** tissue. The former is major glycoprotein bearing .beta.1-6 branched oligosaccharides of breast ***cancer*** and was identical to CEA. The latter 120 kDa glycoprotein belongs to LAP-1, and is highly expressed against type I collagen in vitro. Tumor suppressor gene p53, which has been shown to be altered in breast carcinoma cells, binds to specific DNA sequences and activates transcription from various promoters, and is considered to possess characteristics of a transcription factor. The authors have recently found that wild-type p53 stimulates transcription as well as DNA replication. The mutant p53, however, shows no stimulation of DNA

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replication. Deletion of N-terminal acidic transactivation domain impairs the function to stimulate DNA replication, suggesting that N-terminal and C-terminal regions contribute to p53-mediated stimulation of DNA replication.

L19 ANSWER 41 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 75079532 EMBASE

DOCUMENT NUMBER: 1975079532

TITLE: Searching for human tumor antigens.

AUTHOR: Anderson N.G.; Holladay D.W.; Caton J.E.; et al.

CORPORATE SOURCE: Molec. Anat. Program, Oak Ridge Nat. Lab., Oak Ridge, Tenn.
37830, United States

SOURCE: Cancer Research, (1974) 34/8 (2066-2076).

CODEN: CNREA8

DOCUMENT TYPE: Journal

FILE SEGMENT: 016 Cancer

005 General Pathology and Pathological Anatomy

026 Immunology, Serology and Transplantation

LANGUAGE: English

AB Theoretical considerations are presented leading to recognition of the importance of the isolation and characterization of human tumor associated antigens (especially autoantigens) as central problems in ***cancer*** research and presents a report on progress made in attempts to develop the concepts and methods required to solve these problems. Aside from tumor and tissue extracts, 5 main sources of tumor antigens are considered: the isolated tumor cell membrane, the medium in which tumor cells have grown, serum from tumor patients, the human kidney (from which antigen ***antibody*** complexes may be eluted), and urine from tumor patients. Methods of recovering and concentrating both particulate and soluble fractions are discussed. For separation of soluble materials, the development is charted of automated immunospecific methods, based on cycling immunoabsorption of antigens or antibodies on columns of immobilized antigens or antibodies or ' ***sandwich*** ' columns, and examples are given of separations achieved. The preparation and rationale of use of cascade systems for removing normal substances in the search for abnormal ones are discussed, and the scope of the methods is indicated. Emphasis is placed on the 'amplification' inherent in the method arising from repetitive operation and from the biologic amplification of the immune response in giving in a systematic manner large quantities of antigens and antibodies for use and study.

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(FILE 'HOME' ENTERED AT 15:46:59 ON 10 JUL 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 15:47:09 ON 10 JUL 2001

L1 602627 S MUTATION
 L2 16418 S (IMMUNOASSAY OR ELISA OR ANTIBODY) AND SANDWICH
 L3 313226 S COLORECTAL OR CRC OR COLON
 L4 5 S L1 AND L2 AND L3
 L5 4 DUP REM L4 (1 DUPLICATE REMOVED)
 L6 114159 S GERMLINE OR HERITABLE OR INHERIT##
 L7 0 S L6 AND L2 AND L3
 L8 1432454 S CANCER
 L9 2 S L8 AND L6 AND L2
 L10 2 DUP REM L9 (0 DUPLICATES REMOVED)
 L11 8291 S ATAXIA-TELANGIECTASIA
 L12 0 S L11 AND L6 AND L2
 L13 2371 S HEMANGIOBLASTOMA
 L14 0 S L13 AND L6 AND L2
 L15 856646 S RENAL
 L16 0 S L15 AND L6 AND L2
 L17 34354 S PHEOCHROMOCYTOMA
 L18 0 S L17 AND L6 AND L2
 L19 383793 S GASTROINTESTINAL
 L20 0 S L19 AND L6 AND L2
 L21 537876 S BREAST OR MAMMARY
 L22 1 S L21 AND L6 AND L2
 L23 235597 S OVARIAN
 L24 236011 S OVARY
 L25 1 S (L23 OR L24) AND L6 AND L2
 L26 271519 S ENDOMETRIAL OR UTERINE
 L27 0 S L26 AND L6 AND L2
 L28 199028 S PROSTATE OR PROSTATIC
 L29 0 S L28 AND L6 AND L2
 L30 456817 S PANCREAS OR PANCREATIC
 L31 0 S L30 AND L6 AND L2
 L32 186536 S BILIARY OR BILE DUCT
 L33 0 S L32 AND L6 AND L2
 L34 60847 S CYSTIC FIBROSIS
 L35 0 S L34 AND L6 AND L2
 L36 17888 S DUCHENNE
 L37 0 S L36 AND L6 AND L2
 L38 13408 S GENITOURINARY
 L39 0 S L38 AND L6 AND L2
 L40 31412 S GYNECOLOGIC
 L41 0 S L40 AND L6 AND L2
 L42 689 S EMERY-DREIFUSS
 L43 0 S L42 AND L6 AND L2
 L44 215902 S FANCONI OR ANEMIA
 L45 0 S L44 AND L6 AND L2
 L46 11136 S HUNTER
 L47 0 S L46 AND L6 AND L2
 L48 18054 S NEUROFIBROMATOSIS
 L49 0 S L48 AND L6 AND L2
 L50 148469 S MELANOMA
 L51 0 S L50 AND L6 AND L2
 L52 28316 S POLYCYSTIC
 L53 0 S L52 AND L6 AND L2

L54 1503 S NEVOID
 L55 0 S L54 AND L6 AND L2
 L56 4234 S VON HIPPEL-LINDAU
 L57 0 S L56 AND L6 AND L2
 L58 17055 S L6 AND (L11 OR L13 OR L15 OR L17 OR L19 OR L21 OR L23 OR L1
 L59 4648323 S DIAGNOS? OR SUSCEPTIBIL?
 L60 6270 S L59 AND L58
 L61 1432454 S CANCER
 L62 2718 S L61 AND L60
 L63 1851427 S IMMUNOASSAY OR WESTERN OR IMMUNOBLOT OR ANTIBODY OR MOAB OR M
 L64 93 S L63 AND L62
 L65 52 DUP REM L64 (41 DUPLICATES REMOVED)

L65 ANSWER 1 OF 52 MEDLINE DUPLICATE 1
 ACCESSION NUMBER: 2001179380 MEDLINE
 DOCUMENT NUMBER: 21124830 PubMed ID: 11207365
 TITLE: A human BRCA2 complex containing a structural DNA binding component influences cell cycle progression.
 AUTHOR: Marmorstein L Y; Kinev A V; Chan G K; Bochar D A; Beniya H; Epstein J A; Yen T J; Shiekhattar R
 CORPORATE SOURCE: The Wistar Institute, 3601 Spruce Street, Philadelphia, PA 19104, USA.
 SOURCE: CELL, (2001 Jan 26) 104 (2) 247-57.
 Journal code: CQ4; 0413066. ISSN: 0092-8674.
 PUB. COUNTRY: United States
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200103
 ENTRY DATE: Entered STN: 20010404
 Last Updated on STN: 20010404
 Entered PubMed: 20010306
 Entered Medline: 20010329

AB ***Germline*** mutations of the human BRCA2 gene confer ***susceptibility*** to ***breast*** ***cancer***. Although the function of the BRCA2 protein remains to be determined, murine cells homozygous for BRCA2 inactivation display chromosomal aberrations. We have isolated a 2 MDa BRCA2-containing complex and identified a structural DNA binding component, designated as BRCA2-Associated Factor 35 (BRAF35). BRAF35 contains a nonspecific DNA binding HMG domain and a kinesin-like coiled coil domain. Similar to BRCA2, BRAF35 mRNA expression levels in mouse embryos are highest in proliferating tissues with high mitotic index. Strikingly, nuclear staining revealed a close association of BRAF35/BRCA2 complex with condensed chromatin coincident with histone H3 phosphorylation. Importantly, ***antibody*** microinjection experiments suggest a role for BRCA2/BRAF35 complex in modulation of cell cycle progression.

L65 ANSWER 2 OF 52 MEDLINE DUPLICATE 2
 ACCESSION NUMBER: 2001142380 MEDLINE
 DOCUMENT NUMBER: 21084750 PubMed ID: 11216917
 TITLE: Epidemiological and molecular aspects of ***ovarian*** ***cancer*** risk.
 AUTHOR: Runnebaum I B; Stickeler E
 CORPORATE SOURCE: Department of Obstetrics and Gynecology, University of Freiburg, Germany.. runnebaum@frk.ukl.uni-freiburg.de
 SOURCE: JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY, (2001 Feb) 127 (2) 73-9. Ref: 57
 Journal code: HL5; 7902060. ISSN: 0171-5216.

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PUB. COUNTRY: Germany: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered PubMed: 20010216
Entered Medline: 20010308

AB In ***Western*** and Northern Europe, as well as in the United States, ***ovarian*** ***cancer*** represents the third most frequent ***cancer*** of the female genital tract with an estimated 191,000 newly ***diagnosed*** cases per year worldwide. Due to its insidious onset, the disease is ***diagnosed*** in 70% of cases in an advanced stage. Consequently, ***ovarian*** ***cancer*** is the fifth leading cause of ***cancer*** -related deaths in women. Epidemiological and molecular studies reviewed here have identified demographic, geographic, molecular, genetic, endocrine, dietary, and environmental factors, which affect the risk of developing ***ovarian*** ***cancer*** : ethnic background, tumor suppressor gene mutations in the ***germline*** , positive family history, number of full-term pregnancies [odds ratio (OR): 0.17; 95% confidence interval (CI): 0.05-0.54], time spent ***breast*** feeding, oral contraceptive use [OR: 0.23; 95% CI: 0.1-0.50], unexplained infertility (OR: 2.64; 95% CI: 1.10-6.35), tubal ligation and prior hysterectomy (OR: 0.5; 95% CI: 0.2-0.9), dietary factors and obesity (OR: 1.7; 95% CI: 1.1-2.8). This knowledge provides the objective basis for an individual risk assessment for women, which should lead to sophisticated counseling and prevention. It should also help to individualize the therapeutic approach in the event that disease is ***diagnosed*** .

L65 ANSWER 3 OF 52 MEDLINE

DUPLICATE 3

ACCESSION NUMBER: 2001216729 MEDLINE
DOCUMENT NUMBER: 21156764 PubMed ID: 11258198
TITLE: Pharmacogenetics of human androgens and ***prostatic*** diseases.
AUTHOR: Novelli G; Margiotti K; Sangiuolo F; Reichardt J K
CORPORATE SOURCE: Dipartimento di Biopatologia e Diagnostica per Immagini, Università di Roma Tor Vergata, 00133 Roma, Italy.. novelli@med.uniroma2.it
CONTRACT NUMBER: CA68581 (NCI)
CA83112 (NCI)
SOURCE: Pharmacogenomics, (2001 Feb) 2 (1) 65-72. Ref: 53
Journal code: DOS; 100897350. ISSN: 1462-2416.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20010425
Entered PubMed: 20010321
Entered Medline: 20010419

AB ***Prostate*** ***cancer*** (PCa) and benign ***prostatic*** hypertrophy (BPH) are two common and growing public health problems in the ***Western*** world. We review here the recent biochemical and

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pharmacogenetic literature related to these two ***prostatic*** disorders. We focus first on constitutional (' ***germline*** ') single nucleotide polymorphism (SNPs) at the steroid 5 alpha-reductase (SRD5A2) locus, which encodes the human ***prostatic*** (or Type II) steroid 5 alpha-reductase enzyme. The investigations reviewed point to several uses of personalised medicine at the SRD5A2 locus. In addition, we report on recent identification of somatic pharmacogenetic alterations at the androgen receptor (AR) locus, which encodes the human androgen receptor, suggesting that this also may be a fruitful field of investigation, with important clinical applications. Pharmacogenomic investigation of constitutional and somatic DNA changes in human genes predisposing to ***cancer*** may lead to significant advances in chemoprevention, presymptomatic ***diagnosis*** and improved treatment of PCa.

L65 ANSWER 4 OF 52 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:335428 CAPLUS

DOCUMENT NUMBER: 133:1491

TITLE: Identification of human chromosome 17p-linked ***prostate*** ***cancer*** ***susceptibility*** tumor suppressor gene HPC2 and its therapeutic application

INVENTOR(S): Tavtigian, Sean V.; Teng, David H. F.; Simard, Jacques; Rommens, Johanna M.

PATENT ASSIGNEE(S): Myriad Genetics, Inc., USA

SOURCE: PCT Int. Appl., 157 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000027864	A1	20000518	WO 1999-US26055	19991105
W: AU, CA, JP, KR, NZ, ZA				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

PRIORITY APPLN. INFO.: US 1998-107468 P 19981106 *prov.*

AB A human ***prostate*** ***cancer*** ***susceptibility*** gene HPC2 is identified and mapped to chromosome 17p by assembling related EST sequences and genetic linkage analyses. The complete HPC2 gene (contg. 24 exons and 23 introns) has been sequenced. Addnl., the exon 1 sequence of mouse HPC2 gene is identified in the similar way. Methods and materials used to isolate and detect a human ***prostate*** ***cancer*** predisposing gene (HPC2), some alleles of which cause ***susceptibility*** to ***cancer***, in particular ***prostate*** ***cancer***, and its ***germline*** mutations or somatic mutations are provided. Human HPC2 gene, their allelic variant or mutants, and related protein products can be used in the ***diagnosis*** and prognosis of human ***prostate*** cancers, gene therapy, protein replacement therapy, and drug screening for ***cancer*** therapy.

REFERENCE COUNT: 6

REFERENCE(S): (1) Birren; Gene Sequence 1998
(2) Cooney, K; Journal Of The National Cancer Institute 1997, V89(13), P955 CAPLUS
(3) Cooney, K; Seminars in Urologic Oncology 1998, V16(4), P202 MEDLINE
(5) Jensen; US 5925519 A 1999 CAPLUS
(6) Xu, J; Nature Genetics 1998, V20(2), P175 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

- L65 ANSWER 5 OF 52 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 2000371353 EMBASE
 TITLE: The mismatch repair gene hMSH2 is mutated in the
 prostate ***cancer*** cell line LNCaP.
 AUTHOR: Leach F.S.; Velasco A.; Hsieh J.-T.; Sagalowsky A.I.;
 McConnell J.D.
 CORPORATE SOURCE: F.S. Leach, Urologic Oncology Branch, National Cancer
 Institute, National Institutes of Health, 10 Center Drive,
 Bethesda, MD 20892, United States
 SOURCE: Journal of Urology, (2000) 164/5 (1830-1833).
 Refs: 24
 ISSN: 0022-5347 CODEN: JOURAA
 COUNTRY: United States
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 016 Cancer
 028 Urology and Nephrology
 LANGUAGE: English
 SUMMARY LANGUAGE: English
- AB Purpose: Mismatch repair genes are responsible for the coordinated
 correction of misincorporated nucleotides formed during DNA replication.
 Inactivating and ***inherited*** mutations in the prototypic mismatch
 repair gene hMSH2 have been described in a ***cancer*** predisposition
 syndrome known as hereditary nonpolyposis colon ***cancer***. Patients
 with hereditary nonpolyposis colon ***cancer*** are at increased risk
 for colon ***cancer*** and extracolonic cancers such as upper tract
 transitional cell carcinoma but not ***prostate*** ***cancer***.
 We investigated expression of hMSH2 in ***prostate*** ***cancer***
 cell lines using genetic and molecular analysis. Materials and Methods: We
 used the 3 well described ***prostate*** ***cancer*** cell lines,
 DU145, LNCaP and PC3. ***Western*** blot analysis with monoclonal
 antibody to hMSH2 was used to assess expression. Southern blot and
 polymerase chain reaction of genomic DNA were used to identify genetic
 alterations in the hMSH2 gene. Single cell cloning, dinucleotide repeats
 and BAT-26 were used to assess the cell lines for microsatellite
 instability. Results: The ***prostate*** ***cancer*** cell line
 LNCaP did not express hMSH2 and was found to have a homozygous deletion of
 hMSH2 exons 9 to 16, resulting in truncation of the protein. While
 microsatellite analysis did not reveal alterations at the BAT-26 locus,
 single cell cloning produced several LNCaP subclones with alteration at 1
 dinucleotide repeat. Conclusions: The well described ***prostate***
 cancer cell line LNCaP has a mutation in the hMSH2 gene, resulting
 in loss of expression and possible evidence of microsatellite instability.
 To our knowledge our finding is the first demonstration of a genetic
 alteration in hMSH2 in a ***prostate*** ***cancer*** cell line.
- L65 ANSWER 6 OF 52 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 4
 ACCESSION NUMBER: 2000103688 EMBASE
 TITLE: Frequency of BRCA1/BRCA2 mutations in a population-based
 sample of young ***breast*** carcinoma cases.
 AUTHOR: Malone K.E.; Daling J.R.; Neal C.; Suter N.M.; O'Brien C.;
 Cushing-Haugen K.; Jonasdottir T.J.; Thompson J.D.;
 Ostrander E.A.
 CORPORATE SOURCE: Dr. E.A. Ostrander, Clinical Research Division, Fred
 Hutchinson Can. Research Center, 1100 Fairview Ave. N.,
 Seattle, WA 98109-1024, United States
 SOURCE: Cancer, (15 Mar 2000) 88/6 (1393-1402).
 Refs: 35

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ISSN: 0008-543X CODEN: CANCAR

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics

LANGUAGE: English

SUMMARY LANGUAGE: English

AB BACKGROUND. There is a clear and growing need for data regarding BRCA1 and BRCA2 mutation frequencies among ***breast*** carcinoma cases not specifically ascertained on the basis of extreme family history profiles. Toward this end, the authors previously reported results with regard to BRCA1 in ***breast*** carcinoma patients drawn from a population-based study. In the current study the authors present new findings concerning BRCA2 mutation frequency in this same population, as well as summary data regarding the combined contribution of these two genes. METHODS. Subjects were drawn from two population-based, case-control studies of ***breast*** carcinoma in young women conducted in ***western*** Washington State and focused on 1) women ***diagnosed*** with ***breast*** carcinoma before age 35 years (n = 203); and 2) women with a first-degree family history of ***breast*** carcinoma who were ***diagnosed*** before age 45 years (n = 225). Similarities and differences between BRCA2 carriers and BRCA1 carriers were analyzed in terms of age at ***diagnosis***, family history status, and disease features. RESULTS. Of cases ***diagnosed*** before age 35 years, all of whom were unselected for family history, 9.4% carried ***germline*** mutations (3.4% for BRCA2 and 5.9% for BRCA1). Of cases ***diagnosed*** before age 45 years who had a first-degree family history of ***breast*** carcinoma, 12.0% carried ***germline*** mutations (4.9% for BRCA2 and 7.1% for BRCA1). Increased frequencies of mutations were observed in cases with a personal or family history of early age at ***diagnosis*** and in those with four or more family members affected with ***breast*** carcinoma. BRCA2 mutations were less common than BRCA1 mutations in families with any history of ***ovarian*** carcinoma. CONCLUSIONS. Overall, given current constraints on health care resources, these data suggest that screening for ***germline*** mutations in these ***breast*** carcinoma ***susceptibility*** genes may have the greatest impact on overall health care if it is prioritized toward high and moderate risk populations. (C) 2000 American ***Cancer*** Society.

L65 ANSWER 7 OF 52 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000218155 EMBASE

TITLE: Characteristics of BRCA1 mutations in a population-based case series of ***breast*** and ***ovarian*** ***cancer***.

AUTHOR: Anton-Culver H.; Cohen P.F.; Gildea M.E.; Ziogas A.

CORPORATE SOURCE: H. Anton-Culver, Epidemiology Division, College of Medicine, University of California, Irvine, CA 92697-7550, United States. hantoncu@uci.edu

SOURCE: European Journal of Cancer, (2000) 36/10 (1200-1208). Refs: 30

ISSN: 0959-8049 CODEN: EJCAEL

PUBLISHER IDENT.: S 0959-8049(00)00110-6

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 010 Obstetrics and Gynecology
016 Cancer
017 Public Health, Social Medicine and Epidemiology
022 Human Genetics

LANGUAGE: English

SUMMARY LANGUAGE: English

AB ***Breast*** and ***ovarian*** cancers account for approximately 210 000 newly ***diagnosed*** cases per year. More than half a million American women are estimated to be carriers of a ***breast*** ***cancer*** ***susceptibility*** gene. The purpose of this study was to assess the association of characteristics such as, age at ***diagnosis***, race/ethnicity and family history of ***cancer*** with ***inherited*** BRCA1 mutations in a population-based sample of ***breast*** and ***ovarian*** ***cancer*** cases. No selection was made by race, age at ***diagnosis*** or positive family history of ***breast*** or ***ovarian*** ***cancer***. The population under study was all ***breast*** ***cancer*** cases ***diagnosed*** in Orange County, CA, during the 1-year period beginning 1 March 1994 and all ***ovarian*** ***cancer*** cases ***diagnosed*** in Orange County during the 2-year period beginning 1 March 1994. This report focuses on the first consecutively ascertained 802 participating probands enrolled in the study, of which 9 were male ***breast*** ***cancer*** probands, 673 were female ***breast*** ***cancer*** probands and 120 were ***ovarian*** ***cancer*** probands. We observed 11 BRCA1 mutations or 1.6% (95% CI: 0.8-2.9) among the 673 female ***breast*** ***cancer*** probands and 4 BRCA1 mutations or 3.3% (95% CI: 0.8-8.3) among the 120 ***ovarian*** ***cancer*** probands. No BRCA1 mutations were identified among the 98 non-white ***breast*** and ***ovarian*** ***cancer*** probands. The prevalence of BRCA1 mutations in non-Hispanic-white ***breast*** ***cancer*** cases below the age of 50 years was 2%. Positive family history of ***breast*** or ***ovarian*** cancers was significantly associated with BRCA1 mutation status among ***breast*** ***cancer*** probands. Similarly, positive family history of ***breast*** or ***ovarian*** ***cancer*** was significantly associated with BRCA1 mutation status among the ***ovarian*** ***cancer*** probands. In summary, we present results on the prevalence of BRCA1 mutations in a significantly larger sample of population-based ***breast*** and ***ovarian*** ***cancer*** cases than previously reported. The results indicate that, using a conservative approach to targeted genotyping of BRCA1, the frequency of mutations was consistent with those reported using similar methods of population-based case ascertainment. Copyright (C) 2000.

^ L65 ANSWER 8 OF 52 MEDLINE DUPLICATE 5
 ACCESSION NUMBER: 2000485870 MEDLINE
 DOCUMENT NUMBER: 20487343 PubMed ID: 11034530
 TITLE: Hereditary ***breast*** ***cancer*** : high risk genes, genetic testing and clinical implications.
 — AUTHOR: Hamann U
 — CORPORATE SOURCE: Deutsches Krebsforschungszentrum, Heidelberg, Germany.
 — SOURCE: CLINICAL LABORATORY, (2000) 46 (9-10) 447-61. Ref: 146
 Journal code: DLI; 9705611. ISSN: 1433-6510.
 PUB. COUNTRY: GERMANY: Germany, Federal Republic of
 Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200103
 ENTRY DATE: Entered STN: 20010404
 Last Updated on STN: 20010404

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Entered PubMed: 20010122

Entered Medline: 20010315

AB About one in eight to ten women living in ***Western*** countries will develop ***breast*** ***cancer*** during her lifetime and between 5-10% of these cases result from an ***inherited*** ***susceptibility*** to the disease. Within the past few years, a number of genes associated with a high risk of ***breast*** ***cancer*** have been identified, including BRCA1, BRCA2, TP53, PTEN, MLH1, MSH2, and STK11. The identification of these genes, together with the rapid advances in molecular genetic analyses, should improve the ***diagnosis*** and therapy of ***breast*** ***cancer***. This article reviews the genetic basis of hereditary ***breast*** ***cancer***, in particular the contribution of BRCA1 and BRCA2 and discusses the clinical application of this new molecular knowledge with regard to molecular testing, surveillance and prevention in women with a hereditary predisposition to ***breast*** ***cancer***.

L65 ANSWER 9 OF 52 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 2001:299314 BIOSIS

DOCUMENT NUMBER: PREV200100299314

TITLE: Increased mutation rate in cells from patients with ***ataxia*** - ***telangiectasia*** measured by a new methodology.

AUTHOR(S): Araten, David J. (1); Thaler, Howard (1); Luzzatto, Lucio (1)

CORPORATE SOURCE: (1) Departments of Human Genetics and Hematology, Memorial Sloan-Kettering Cancer Center, New York, NY USA

SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 2, pp. 170b. print.

Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology . ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Since malignant transformation results from a sequence of discrete mutational events, the probability of a cell becoming malignant is expected, in first approximation, to be proportional to rn , where r is the mutation rate per cell division and n is the number of mutations in critical genes required for transformation. The value of r may be increased due to environmental agents or it may be increased due to ***inherited*** factors. Indeed, it has been suggested that r may be increased in some ***inherited*** ***cancer*** ***susceptibility*** syndromes, such as ***ataxia*** - ***telangiectasia*** (AT). We have developed a novel technique to measure r using as a model the X-linked PIG-A gene, whose function is essential for the expression of glycosylphosphatidylinositol (GPI)-linked membrane proteins. B lymphoblastoid cell lines are first stained with an ***antibody*** specific for CD59 (a GPI-linked protein), and the upper 50th percentile are collected by FACS to eliminate pre-existing mutants: After growth in culture for at least 1 week, the number of cell divisions (d) is estimated from appropriate cell counts, and the cells are then stained for flow cytometric analysis with a mixture of antibodies specific for CD48, CD55, and CD59 (all GPI-linked proteins). Thus, we can determine the mutant frequency (f), from which the mutation rate is calculated as $r = f/d$. In a panel of 8 normal cell lines, the median r was 7.5×10^{-7} (range 2.4 to 30×10^{-7}). (This value is remarkably close to that resulting from estimating the mutation rate in the *hprt* gene in

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normal individuals.) In cell lines from 14 patients with AT, the median r was 17.7×10^{-7} (range 3.7 to 270×10^{-7}). While the majority of AT cell lines had r values in the normal range, there was, overall, an upward shift, and some had a very high mutation rate. We conclude that in some AT patients, r is increased, which may account for malignancies arising at an early age in some patients with this disorder.

L65 ANSWER 10 OF 52 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 2001:21298 BIOSIS

DOCUMENT NUMBER: PREV200100021298

TITLE: Cell-cycle dysregulation in ***breast*** ***cancer***
: ***Breast*** ***cancer*** therapies targeting the
cell cycle.

AUTHOR(S): Zafonte, Brian T. (1); Hulit, James; Amanatullah, Derek F.;
Albanese, Chris; Wang, Chenguang; Rosen, Eliot; Reutens,
Anne; Sparano, Joseph A.; Lisanti, Michael P.; Pestell,
Richard G.

CORPORATE SOURCE: (1) Department of Development and Molecular Biology,
Division of Hormone-Dependent Tumor Biology, The Albert
Einstein Comprehensive Cancer Center, Albert Einstein
College of Medicine, Bronx, NY, 10461 USA

SOURCE: Frontiers in Bioscience, (Dec. 1, 2000) Vol. 5, No. CITED
DEC. 13, 2000, pp. 1-42. <http://www.bioscience.org/2000/v5/d/zafonte/fulltext.htm> cited December 15, 2000
<http://www.bioscience.org/>. online.

DOCUMENT TYPE: Article; General Review

LANGUAGE: English

SUMMARY LANGUAGE: English

AB ***Breast*** ***cancer*** is the most commonly ***diagnosed***
cancer in American women. The underlying mechanisms that cause
aberrant cell proliferation and tumor growth involve conserved pathways,
which include components of the cell cycle machinery. Proto-oncogenes,
growth factors, and steroids have been implicated in the pathogenesis of
breast ***cancer***. Surgery, local irradiation, and
chemotherapy have been the mainstay of treatment for early and advanced
stage disease. Potential targets for selective ***breast***
cancer therapy are herein reviewed. Improved understanding of the
biology of ***breast*** ***cancer*** has led to more specific
"targeted therapies" directed at biological processes that are selectively
deregulated in the cancerous cells. Examples include tamoxifen for
estrogen receptor positive tumors and immunoneutralizing antibodies such as
trastuzumab for Her2/neu overexpressing tumors. Other novel anticancer
agents such as paclitaxel, a microtubule binding molecule, and
flavopiridol, a cyclin dependent kinase inhibitor, exert their anticancer
effects by inhibiting cell cycle progression.

L65 ANSWER 11 OF 52 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 6

ACCESSION NUMBER: 1999343376 EMBASE

TITLE: Mouse models for colorectal ***cancer***.

AUTHOR: Heyer J.; Yang K.; Lipkin M.; Edelmann W.; Kucherlapati R.

CORPORATE SOURCE: R. Kucherlapati, Department of Molecular Genetics, Albert
Einstein College of Medicine, 1300 Morris Park Avenue,
Bronx, NY 10461, United States

SOURCE: Oncogene, (20 Sep 1999) 18/38 (5325-5333).

Refs: 76

ISSN: 0950-9232 CODEN: ONCNES

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer

022 Human Genetics
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Colorectal ***cancer*** (CRC) is one of the most common cancers in the ***Western*** world. Much has been learned about colorectal ***cancer*** from human ***inherited*** syndromes, such as familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal ***cancer*** (HNPCC). Mouse models for CRC were generated by introducing mutations into the mouse genes, whose human counterparts were implicated in the onset and progression of CRC. Central among these are mice carrying mutations in the Adenomatous polyposis coli (Apc) gene. Although most of these Apc mutations share some common phenotypes as homozygous embryonic lethality and tumor predisposition, the severity of the tumor predisposition is variable. Mice with mutations in the mismatch repair genes, Msh2 and Mlh1, exhibit a mismatch repair defect and are predisposed to developing ***gastrointestinal*** ***cancer***, lymphomas and tumors of other organ systems. Mice carrying a mutation in the Pms2 gene are predisposed to lymphomas and other tumors. Mice with a mutation in the Msh6 gene have a defect in base mismatch repair and show a tumor predisposition phenotype. Mice with mutations in Mlh1, Pms2 and Msh5 have defects in meiosis suggesting unique roles for these genes in gametogenesis.

L65 ANSWER 12 OF 52 MEDLINE

DUPLICATE 7

ACCESSION NUMBER: 1999228528 MEDLINE

DOCUMENT NUMBER: 99228528 PubMed ID: 10213514

TITLE: Distinct molecular pathogeneses of early-onset ***breast*** cancers in BRCA1 and BRCA2 mutation carriers: a population-based study.

AUTHOR: Armes J E; Trute L; White D; Southey M C; Hammet F; Tesoriero A; Hutchins A M; Dite G S; McCredie M R; Giles G G; Hopper J L; Venter D J

CORPORATE SOURCE: Molecular Pathology Laboratory, Victorian Breast Cancer Research Consortium, Peter MacCallum Cancer Institute, East Melbourne, Victoria, Australia.

SOURCE: CANCER RESEARCH, (1999 Apr 15) 59 (8) 2011-7.
Journal code: CNF; 2984705R. ISSN: 0008-5472.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199906

ENTRY DATE: Entered STN: 19990618

Last Updated on STN: 19990618

Entered Medline: 19990607

AB ***Breast*** cancers arising in women with and without a ***germline*** mutation in the BRCA1 or BRCA2 gene display different histological features, which suggests unique mechanisms of molecular pathogenesis: We used a molecular pathological analysis to define the genetic abnormalities relevant to these specific pathogeneses. Tumor material was studied from 40 women with ***breast*** ***cancer*** ***diagnosed*** before 40 years of age, sampled from a population-based study and stratified by BRCA1 and BRCA2 ***germline*** mutation status. Cases were not selected for family history or ethnic origin, and none were known to be genetically related. Thus, ***germline*** mutation itself is likely to impact on the molecular pathogenesis of these tumors, with no substantial influence due to modifying genetic or environmental factors. ***Breast*** cancers occurring in BRCA1

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mutation carriers had significantly higher levels of p53 expression, including the preinvasive (carcinoma in situ) stage of disease, compared with cancers occurring in BRCA2 mutation carriers or women with no detectable ***germline*** mutation. These cancers also had a higher proliferation rate as measured by Ki-67 ***antibody***. Expression of the prognostic factors c-erbB-2, cyclin D1, and estrogen receptor was significantly less common in BRCA1 mutation carriers. Lower levels of cyclin D1 were also found in cancers from BRCA2 mutation carriers compared with non-mutation carriers. Direct p53 mutation analysis revealed mutations in 18% of all of the early-onset ***breast*** cancers within the study and included rare insertion and deletional mutations in cancers from BRCA1 mutation carriers. Our data indicate that a BRCA1 ***breast*** ***cancer*** phenotype may be recognized by an exceptionally high proliferation rate and early and frequent p53 overexpression but infrequent selection for overexpression of several other prognostic factor proteins known to be involved in ***breast*** oncogenesis. In contrast, ***breast*** cancers arising in BRCA2 mutation carriers have a more heterogeneous phenotypic profile.

L65 ANSWER 13 OF 52 MEDLINE DUPLICATE 8
 ACCESSION NUMBER: 1999432761 MEDLINE
 DOCUMENT NUMBER: 99432761 PubMed ID: 10503143
 TITLE: Chronic pancreatitis and other risk factors for
 pancreatic ***cancer***
 AUTHOR: Lowenfels A B; Maisonneuve P; Lankisch P G
 CORPORATE SOURCE: Department of Surgery, New York Medical College, Valhalla,
 USA.. Lowenfel@NYMC.edu
 SOURCE: GASTROENTEROLOGY CLINICS OF NORTH AMERICA, (1999 Sep) 28
 (3) 673-85, x. Ref: 67
 Journal code: GNA; 8706257. ISSN: 0889-8553.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199911
 ENTRY DATE: Entered STN: 20000111
 Last Updated on STN: 20000111
 Entered Medline: 19991109

AB ***Pancreatic*** ***cancer*** is the fourth or fifth most common
 form of ***cancer*** in ***Western*** countries. Early
 diagnosis is difficult and the overall mortality rate is high.
 Individuals at high risk for ***pancreatic*** ***cancer*** include
 smokers, African-Americans, and persons with various types of
 pancreatitis. As with other cancers, dietary factors play an important
 role. Approximately 10% of all ***pancreatic*** tumors may be related
 to an ***inherited*** germ line disorder.

L65 ANSWER 14 OF 52 MEDLINE DUPLICATE 9
 ACCESSION NUMBER: 1999263472 MEDLINE
 DOCUMENT NUMBER: 99263472 PubMed ID: 10329039
 TITLE: Telomeric instability and reduced proliferative potential
 in ***ovarian*** surface epithelial cells from women
 with a family history of ***ovarian*** ***cancer***
 .
 AUTHOR: Kruk P A; Godwin A K; Hamilton T C; Auersperg N
 CORPORATE SOURCE: Department of Pathology, University of South Florida,
 Tampa, Florida 33612, USA.. pkruk@com1.med.usf.edu

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SOURCE: GYNECOLOGIC ONCOLOGY, (1999 May) 73 (2) 229-36.
Journal code: FXC; 0365304. ISSN: 0090-8258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990628
Last Updated on STN: 19990628
Entered Medline: 19990614

AB OBJECTIVE: Increased telomeric instability in normal ***ovarian*** surface epithelium may contribute to ***ovarian*** carcinogenesis in women from families with a high frequency of ***breast*** / ***ovarian*** ***cancer*** . To test this hypothesis, we compared proliferative potential, mean telomeric length, and telomerase activity in SV-40 large T-antigen transfected cell lines derived from normal ***ovarian*** surface epithelium of women with and without a familial history of ***breast*** / ***ovarian*** ***cancer*** . METHODS: Telomeric instability was examined in SV-40 large T-antigen transfected cell lines of normal ***ovarian*** surface epithelium from patients with (FHIOSE, N = 5) and without (NFHIOSE, N = 11) a history of familial ***breast*** / ***ovarian*** ***cancer*** . The duration and total attainable number of population doublings, mean telomeric length, rate of telomeric loss, and telomerase activity were determined by cell counts, Southern blot analysis, and PCR ***ELISA*** . RESULTS: FHIOSE cells attained fewer population doublings than NFHIOSE cells and doubled at approximately half the rate of NFHIOSE cells, indicating a reduced proliferative capacity in FHIOSE cells. While telomerase activity was not detected in FHIOSE or NFHIOSE cell lines, mean telomeric lengths in FHIOSE were generally 1 kb shorter than in NFHIOSE cells and the rate of telomeric loss as a function of population doublings was up to threefold greater in FHIOSE cells. CONCLUSIONS: Increased telomeric instability and reduced growth potential suggest greater proximity to replicative senescence in ***ovarian*** surface epithelium from women with a familial history of ***breast*** / ***ovarian*** ***cancer*** . Consequently, an accumulation of genetic aberrations due to accelerated cellular aging may contribute to the enhanced ***susceptibility*** for malignant transformation and earlier onset in ***heritable*** ***ovarian*** ***cancer*** .
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L65 ANSWER 15 OF 52 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1999365864 MEDLINE
DOCUMENT NUMBER: 99365864 PubMed ID: 10436811
TITLE: Biliopancreatic malignancy: screening the at risk patient with molecular markers.
AUTHOR: Caldas C
CORPORATE SOURCE: University of Cambridge, Department of Oncology, UK.. cc234@cam.ac.uk
SOURCE: ANNALS OF ONCOLOGY, (1999) 10 Suppl 4 153-6. Ref: 42
Journal code: AYF; 9007735. ISSN: 0923-7534.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19990921

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Last Updated on STN: 19990921

Entered Medline: 19990909

AB Biliopancreatic malignancy is one of the leading causes of ***cancer*** death in the ***Western*** world. Defining at risk groups has been difficult. Diabetes mellitus and pancreatitis increase the risk of ***pancreatic*** carcinoma, and inflammatory bowel disease and associated sclerosing colangitis increase the risk of ***biliary*** tract malignancy. ***Pancreatic*** carcinoma has also been described in pedigrees with ***inherited*** ***cancer*** predisposition. Extensive molecular profiling of ***pancreatic*** carcinomas has been accomplished over the past few years, but similar knowledge in other biliopancreatic malignancies is lacking. In almost all ***pancreas*** cancers at least one alteration will occur out of a combination of K-ras mutations and inactivation of the tumor suppressor genes p16/MTS1/ink4a, p53 and DPC4/Smad4. Mutations of K-ras and p16 have been described in hyperplastic and dysplastic ***pancreatic*** ductal lesions believed to be the non-malignant precursors of ***pancreatic*** carcinoma. Detection of K-ras mutations in clinical samples (biliopancreatic secretions, stool, duodenal aspirates, and blood) identical to ones present in primary ***pancreatic*** cancers and/or their precursor ductal lesions has been reported in pilot studies. Recently detection of 18q deletions (at the DPC4 locus) in ***pancreatic*** secretions from early ***pancreatic*** cancers was also reported. These advances raise the possibility that within well defined at risk groups it will be possible to use a combined set of molecular markers to screen clinical samples and detect early ***pancreatic*** ***cancer*** or even pre-malignant lesions. The fulfillment of this promise will depend on proving the role of molecular screening in decreasing morbidity and mortality, which will require well designed clinical studies.

L65 ANSWER 16 OF 52 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:785615 CAPLUS

DOCUMENT NUMBER: 130:34006

TITLE: Human and mouse multiple tumor suppressor MTS1 and MTS2 genes and their ***diagnostic*** and therapeutic uses in ***cancer***

INVENTOR(S): Stone, Steven; Jiang, Ping; Kamb, Alexander

PATENT ASSIGNEE(S): Myriad Genetics Inc., USA

SOURCE: U.S., 80 pp., Cont.-in-part of U.S. 5,739,027.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5843756	A	19981201	US 1995-508735	19950728
US 5739027	A	19980414	US 1995-487033	19950607
US 6210949	B1	20010403	US 1998-201139	19981130
PRIORITY APPLN. INFO.:			US 1995-487033	A2 19950607
			US 1994-214582	B2 19940318
			US 1994-215086	B2 19940318
			US 1994-215087	B2 19940318
			US 1994-227369	B2 19940414
			US 1994-251938	B2 19940601
			WO 1995-US3316	A2 19950317
			US 1995-508735	A3 19950728

AB The present invention relates to the Multiple Tumor Suppressor (MTS) genes

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in mice, their expression products, and their homol. to the human MTS genes. Human and mouse cDNA and deduced protein sequences are provided for MTS1 (p16) and a variant (MTS1E1.beta.) and for a second MTS2 gene (p15). The human MTS genes are involved in human cancers. The invention is further related to the use of the MTS genes in the therapy, ***diagnosis***, and prognosis of human ***cancer***. The invention further relates to mutations in the MTS gene and their use in the ***diagnosis*** of predisposition to ***melanoma***, leukemia, astrocytoma, glioblastoma, lymphoma, glioma, Hodgkin's lymphoma, CLL, and cancers of the ***pancreas***, ***breast***, thyroid, ***ovary***, uterus, testis, kidney, stomach and rectum. The invention also relates to the therapy of human cancers which have a mutation in the MTS gene, including gene therapy, protein replacement therapy, and protein mimetics. Finally, the invention relates to the screening of drugs for ***cancer*** therapy.

REFERENCE COUNT: 25

REFERENCE(S): (1) Aaronson, S; Science 1991, V254, P1146 CAPLUS
(2) Anon; WO 94/09135 1994 CAPLUS
(3) Anon; WO 95/28483 1995 CAPLUS
(4) Cairns, P; Cancer Research 1994, V54, P1422 CAPLUS
(5) Cannon-Albright, L; Genomics 1994, V23, P265 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L65 ANSWER 17 OF 52 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:774140 CAPLUS

DOCUMENT NUMBER: 130:21377

TITLE: ***Diagnosis*** and prognosis of ***cancer*** based on detection of mutations and polymorphisms in the human tumor suppressor gene pRb2/p130

INVENTOR(S): Giordano, Antonio

PATENT ASSIGNEE(S): Thomas Jefferson University, USA

SOURCE: U.S., 77 pp.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5840506	A	19981124	US 1997-832877	19970404

AB The invention provides ***diagnostic*** and prognostic methods which comprise detg. the level of expression of the tumor suppressor gene pRb2/p130. Because the relative level of pRb2/p130 expression correlates with the presence of ***cancer***, tumor grade, and patient prognosis, these methods may be used to detect ***cancer***, to make treatment decisions, to predict patient outcome, and to predict the risk of ***cancer*** in disease-free individuals. The invention further provides methods for the detection of mutations and polymorphisms in the pRb2/p130 gene, which may be used to characterize genetic events assocd. with tumor formation, to trace the parental origin of mutations, to identify carriers of ***germline*** mutations, and to identify individuals with a predisposition to ***cancer***. The human pRb2/p130 gene and its promoter has been cloned and sequenced, and shown to contain 22 exons and 21 introns, spanning >50 kb of genomic DNA. The location and size of each exon and intron of pRb2/p130, as well as the nucleotide sequences at the exon-intron junctions, are provided. PCR primers are provided for amplification of each of the gene exons and the

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promoter region, which can be used for the detection of mutations.

REFERENCE COUNT: 18
 REFERENCE(S): (1) Anon; EP 0390530 1990 CAPLUS
 (3) Baldi; Journal of Cellular Biochemistry 1995, V59, P402 CAPLUS
 (5) Claudio; Cancer Research 1994, V54, P5556 CAPLUS
 (8) Esposito; International Journal of Oncology 1996, V9, P439 CAPLUS
 (10) Giordano; US 5532340 1996 CAPLUS
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L65 ANSWER 18 OF 52 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:333572 CAPLUS

DOCUMENT NUMBER: 129:1442

TITLE: Human chromosome 17q-linked ***breast*** and
 ovarian ***cancer***
 susceptibility gene BRCA1

INVENTOR(S): Skolnick, Mark H.; Goldgar, David E.; Miki, Yoshio;
 Swenson, Jeff; Kamb, Alexander; Harshman, Keith D.;
 Shattuck-Eidens, Donna M.; Tavtigian, Sean V.;
 Wiseman, Roger W.; Futreal, P. Andrew; et al.

PATENT ASSIGNEE(S): Myriad Genetics, Inc., USA; University of Utah
 Research Foundation; United States Dept. of Health and
 Human Services

SOURCE: U.S., 100 pp. Cont.-in-part of U.S. Ser. No. 409,305,
 abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5753441	A	19980519	US 1996-488011	19960105
CN 1169753	A	19980107	CN 1995-195259	19950811
PRIORITY APPLN. INFO.:			US 1994-289221	B2 19940812
			US 1994-300266	B2 19940902
			US 1994-308104	B2 19940916
			US 1994-348824	B2 19941129
			US 1995-409305	B2 19950324

AB The present invention relates to methods and materials used to isolate and detect a human ***breast*** and ***ovarian*** ***cancer*** predisposing gene (BRCA1), some mutant alleles of which cause ***susceptibility*** to ***cancer***, in particular ***breast*** and ***ovarian*** ***cancer***. More specifically, the invention relates to ***germline*** mutations in the BRCA1 gene and their use in the ***diagnosis*** of predisposition to ***breast*** and ***ovarian*** ***cancer***. The present invention further relates to somatic mutations in the BRCA1 gene in human ***breast*** and ***ovarian*** ***cancer*** and their use in the ***diagnosis*** and prognosis of human ***breast*** and ***ovarian*** ***cancer***. Addnl., the invention relates to somatic mutations in the BRCA1 gene in other human cancers and their use in the ***diagnosis*** and prognosis of human cancers. The mutations in the BRCA1 gene include a deletion of nucleotide residues 189-199 in the complete 24,026-residues gene sequence provided. Primers are available for detg. the nucleotide sequence of BRCA1 gene by PCR. The invention also relates to the therapy of human cancers which have a mutation in the BRCA1 gene, including gene

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therapy, protein replacement therapy and protein mimetics. The invention further relates to the screening of drugs for ***cancer*** therapy. Finally, the invention relates to the screening of the BRCA1 gene for mutations, which are useful for ***diagnosing*** the predisposition to ***breast*** and ***ovarian*** ***cancer***.

L65 ANSWER 19 OF 52 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:62187 CAPLUS

DOCUMENT NUMBER: 128:124505

TITLE: Method for ***diagnosing*** a predisposition for ***breast*** and ***ovarian*** ***cancer***

INVENTOR(S): Skolnick, Mark H.; Goldgar, David E.; Miki, Yoshio; Swenson, Jeff; Kamb, Alexander; Harshman, Keith D.; Shattuck-Eidens, Donna M.; Tavtigian, Sean V.; Wiseman, Roger W.; Futreal, P. Andrew; et al.

PATENT ASSIGNEE(S): Myriad Genetics, Inc., USA; University of Utah Research Foundation; United States Dept. of Health and Human Services

SOURCE: U.S., 99 pp. Cont.-in-part of U.S. Ser. No. 409,305, abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5710001	A	19980120	US 1995-487002	19950607
CA 2196790	AA	19960222	CA 1995-2196790	19950811
CA 2196795	AA	19960222	CA 1995-2196795	19950811
WO 9605307	A2	19960222	WO 1995-US10203	19950811
WO 9605307	A3	19960314		
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
WO 9605308	A1	19960222	WO 1995-US10220	19950811
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
EP 699754	A1	19960306	EP 1995-305602	19950811
EP 699754	B1	20010110		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AU 9532428	A1	19960307	AU 1995-32428	19950811
AU 691958	B2	19980528		
AU 9533216	A1	19960307	AU 1995-33216	19950811
AU 691331	B2	19980514		
EP 705902	A1	19960410	EP 1995-305601	19950811
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1159829	A	19970917	CN 1995-195311	19950811
CN 1169753	A	19980107	CN 1995-195259	19950811
JP 10505742	T2	19980609	JP 1995-507508	19950811
AT 198623	E	20010115	AT 1995-305602	19950811
ES 2154712	T3	20010416	ES 1995-305602	19950811
FI 9700514	A	19970407	FI 1997-514	19970207

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FI 9700515	A	19970407	FI 1997-515	19970207
NO 9700625	A	19970414	NO 1997-625	19970211
NO 9700626	A	19970414	NO 1997-626	19970211
PRIORITY APPLN. INFO.:			US 1994-289221	B2 19940812
			US 1994-300266	B2 19940902
			US 1994-308104	B2 19940916
			US 1994-348824	B2 19941129
			US 1995-409305	B2 19950324
			US 1995-483554	A 19950607
			US 1995-487002	A 19950607
			US 1995-488011	A 19950607
			WO 1995-US10203	W 19950811
			WO 1995-US10220	W 19950811

AB The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human ***breast*** and ***ovarian*** ***cancer*** predisposing gene (BRCA1), some mutant alleles of which cause ***susceptibility*** to ***cancer***, in particular ***breast*** and ***ovarian*** ***cancer***. More specifically, the invention relates to ***germline*** mutations in the BRCA1 gene and their use in the ***diagnosis*** of predisposition to ***breast*** and ***ovarian*** ***cancer***. The present invention further relates to somatic mutations in the BRCA1 gene in human ***breast*** and ***ovarian*** ***cancer*** and their use in the ***diagnosis*** and prognosis of human ***breast*** and ***ovarian*** ***cancer***. Addnl., the invention relates to somatic mutations in the BRCA1 gene in other human cancers and their use in the ***diagnosis*** and prognosis of human cancers. The invention also relates to the therapy of human cancers which have a mutation in the BRCA1 gene, including gene therapy, protein replacement therapy and protein mimetics. The invention further relates to the screening of drugs for ***cancer*** therapy. Finally, the invention relates to the screening of the BRCA1 gene for mutations, which are useful for ***diagnosing*** the predisposition to ***breast*** and ***ovarian*** ***cancer***.

L65 ANSWER 20 OF 52 CAPLUS COPYRIGHT 2001 ACS
 ACCESSION NUMBER: 1998:62185 CAPLUS
 DOCUMENT NUMBER: 128:124534
 TITLE: In vivo mutations and polymorphisms in the 17q-linked ***breast*** and ***ovarian*** ***cancer*** ***susceptibility*** gene BRCA1
 INVENTOR(S): Shattuck-Eidens, Donna M.; Simard, Jacques; Durocher, Francine; Emi, Mitsuuru; Nakamura, Yusuke
 PATENT ASSIGNEE(S): Myriad Genetics Inc., USA; Centre de Recherche du Chul; Cancer Institute
 SOURCE: U.S., 103 pp. Cont.-in-part of U.S. Ser. No. 409,305, abandoned.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 7
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
→ US 5709999	A	19980120	US 1995-483553	19950607
CA 2196797	AA	19960222	CA 1995-2196797	19950811
WO 9605306	A2	19960222	WO 1995-US10202	19950811

WO 9605306 A3 19960314
 W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG,
 KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO,
 RU, SD, SI, SK, TJ, TT, UA, UZ, VN
 RW: KE, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE,
 SN, TD, TG

AU 9533212 A1 19960307 AU 1995-33212 19950811
 AU 686004 B2 19980129
 EP 705903 A1 19960410 EP 1995-305605 19950811
 EP 705903 B1 20010523

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
 CN 1169753 A 19980107 CN 1995-195259 19950811
 CN 1172502 A 19980204 CN 1995-195413 19950811
 FI 9700513 A 19970407 FI 1997-513 19970207
 NO 9700624 A 19970414 NO 1997-624 19970211

PRIORITY APPLN. INFO.:

US 1994-289221 B2 19940812
 US 1994-300266 B2 19940902
 US 1994-308104 A2 19940916
 US 1994-348824 B2 19941129
 US 1995-409305 B2 19950324
 US 1995-480784 A 19950607
 US 1995-483553 A 19950607
 WO 1995-US10202 W 19950811

AB The human gene BRCA1 involved in predisposition to ***breast*** and
 ovarian ***cancer*** is cloned and characterized and somatic
 and ***germline*** mutations that may play a role in carcinogenesis
 are characterized. Methods for detection of mutation in the gene are also
 described. Characterization of mutations in BRCA1 assocd. with specific
 human cancers may allow for therapy including gene therapy, protein
 replacement therapy and protein mimetics (no data). The invention further
 relates to the screening of drugs for ***cancer*** therapy. Finally,
 the invention relates to the screening of the BRCA1 gene for mutations,
 which are useful for ***diagnosing*** the predisposition to
 breast and ***ovarian*** ***cancer***.

L65 ANSWER 21 OF 52 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:246200 CAPLUS

DOCUMENT NUMBER: 129:52794

TITLE: Two Li-Fraumeni syndrome families with novel
 germline p53 mutations: loss of the wild-type
 p53 allele in only 50% of tumors

AUTHOR(S): Sedlacek, Z.; Kodet, R.; Kriz, V.; Seemanova, E.;
 Vodvarka, P.; Wilgenbus, P.; Mares, J.; Poustka, A.;
 Goetz, P.

CORPORATE SOURCE: Institute of Biology and Medical Genetics, Second
 Medical School, Charles University, Prague, 15006,
 Czech Rep.

SOURCE: Br. J. Cancer (1998), 77(7), 1034-1039

CODEN: BJCAAI; ISSN: 0007-0920

PUBLISHER: Churchill Livingstone

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We describe two Li-Fraumeni syndrome families. Family A was remarkable
 for two early childhood cases of adrenocortical tumors, family B for a
 high incidence of many characteristic cancers, including a childhood case
 of choroid plexus tumor. Using direct sequencing, we analyzed exons 5-9
 of the p53 gene in constitutional DNA of individuals from both families
 and found two novel ***germline*** mutations in exon 5. In family A,
 we detected a point substitution in codon 138 (GCC to CCC), which resulted

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in the replacement of the alanine by a proline residue. Family B harbored a single-base pair deletion in codon 178 (CAC to -AC), resulting in a frame-shift and premature chain termination. Three out of six tumors examd. from both families, a ***renal*** cell carcinoma, a rhabdomyosarcoma and a ***breast*** ***cancer***, showed loss of heterozygosity and contained only the mutant p53 allele. The remaining three neoplasms, both adrenocortical tumors and the choroid plexus tumor retained heterozygosity. Immunohistochem. with anti-p53 ***antibody*** confirmed accumulation of p53 protein in tumors with loss of heterozygosity, while the remaining tumors were p53 neg. These results support the view that complete loss of activity of the wild-type p53 need not be the initial event in the formation of all tumors in Li-Fraumeni individuals.

L65 ANSWER 22 OF 52 MEDLINE

DUPLICATE 11

ACCESSION NUMBER: 1998204326 MEDLINE

DOCUMENT NUMBER: 98204326 PubMed ID: 9544766

TITLE: BRCA1 mutations and ***breast*** ***cancer*** in the general population: analyses in women before age 35 years and in women before age 45 years with first-degree family history.

COMMENT: Comment in: JAMA. 1998 Mar 25;279(12):955-7

Comment in: JAMA. 1998 Oct 14;280(14):1227-8

AUTHOR: Malone K E; Daling J R; Thompson J D; O'Brien C A; Francisco L V; Ostrander E A

CORPORATE SOURCE: Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Wash 98109-1024, USA..
kmalone@fhcrc.org

CONTRACT NUMBER: N01-CP-95671 (NCI)
R01-CA-41416 (NCI)
R01-CA-63705 (NCI)
+

SOURCE: JAMA, (1998 Mar 25) 279 (12) 922-9.

Journal code: KFR; 7501160. ISSN: 0098-7484.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199804

ENTRY DATE: Entered STN: 19980422

Last Updated on STN: 20000303

Entered Medline: 19980415

AB CONTEXT: Studies of high-risk families with multiple early-onset cases of ***breast*** ***cancer*** have been useful for assessing the type and spectrum of ***germline*** mutations on the BRCA1 gene, but do not provide guidance to women with modest family history profiles. Thus, studies of women from the general population are needed to determine the BRCA1 mutation frequency in women perceived to be at high risk, and to develop profiles of those most likely to be carriers. OBJECTIVE: To characterize frequency and spectrum of ***germline*** BRCA1 mutations in 2 categories of women identified via population-based studies hypothesized to be at increased risk of carrying such mutations: those ***diagnosed*** as having ***breast*** ***cancer*** before age 35 years and those ***diagnosed*** before age 45 years who have first-degree ***breast*** ***cancer*** family history. DESIGN: Study subjects were drawn from 2 population-based case-control studies of ***breast*** ***cancer*** in young women on the basis of their family history or their age of ***diagnosis***. Cases were younger than 35 years or were younger than 45 years with first-degree family

history at the time of ***breast*** ***cancer*** ***diagnosis*** and were ascertained via a population-based ***cancer*** registry, and controls (women without ***breast*** ***cancer***) were identified via random-digit dialing. SETTING: Three counties in ***western*** Washington State. MAIN OUTCOME MEASURE: BRCA1 ***germline*** mutations in study subjects identified in DNA from peripheral blood lymphocytes by single-strand conformation polymorphism analysis using primer pairs that span the BRCA1 coding region and intron-exon boundaries. RESULTS: Of 193 women ***diagnosed*** as having ***breast*** ***cancer*** before age 35 years, none of whom were selected on the basis of family history status, 12 (6.2%, 95% confidence interval [CI], 3.2%-10.6%) had ***germline*** BRCA1 mutations. In 208 women ***diagnosed*** before age 45 years who had first-degree ***breast*** ***cancer*** family history, 15 (7.2%, 95% CI, 4.1%-11.6%) had ***germline*** mutations in BRCA1. In both groups, there were variations in mutation frequency noted by age and by family history. Mutation frequency decreased with increasing age of ***diagnosis***. Higher proportions of mutations were seen in cases with at least 1 relative ***diagnosed*** as having ***breast*** ***cancer*** before age 45 years, in cases with greater numbers of affected relatives, and those with ***ovarian*** ***cancer*** family history. Mutation frequency did not vary by bilateral ***breast*** ***cancer*** family history. No frameshift or nonsense mutations were observed in 71 control women with a first-degree family history, although missense changes of unknown significance were seen in cases and controls. CONCLUSIONS: Women with BRCA1 ***germline*** mutations lacked a common family history profile. Also, a large proportion of the women with a first-degree ***breast*** ***cancer*** family history and women ***diagnosed*** as having ***breast*** ***cancer*** before age 35 years did not carry ***germline*** BRCA1 mutations. Hence, while early-onset disease and a strong ***breast*** ***cancer*** family history may be useful guidelines for checking BRCA1 status, these findings on women drawn from the general population suggest that it may be difficult to develop BRCA1 mutation screening criteria among women with modest family history profiles.

L65 ANSWER 23 OF 52 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998231155 EMBASE

TITLE: Steroid receptors in hereditary ***breast*** carcinomas associated with BRCA1 or BRCA2 mutations or unknown ***susceptibility*** genes.

AUTHOR: Loman N.; Johannsson O.; Bendahl P.-O.; Borg A.; Ferno M.; Olsson H.

CORPORATE SOURCE: Dr. N. Loman, Jubileum Institute, Department of Oncology, University Hospital, S-221 85 Lund, Sweden

SOURCE: Cancer, (15 Jul 1998) 83/2 (310-319).

Refs: 49

ISSN: 0008-543X CODEN: CANCAR

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer

022 Human Genetics

LANGUAGE: English

SUMMARY LANGUAGE: English

AB BACKGROUND. The expression of steroid receptors is a common feature of both male and female ***breast*** carcinomas and is also one of the most important prognostic factors for patients with this disease. Steroid receptor levels in BRCA1-related ***breast*** carcinoma have reportedly been low. Little data on steroid receptor levels have been

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reported with regard to BRCA2. METHODS. Steroid receptor levels were analyzed in 27 ***breast*** carcinomas associated with BRCA1 mutations, 14 associated with BRCA2 mutations, and 32 from individuals who had hereditary ***breast*** carcinoma but no detectable mutations of either BRCA1 or BRCA2. ***Breast*** carcinomas from 32 consecutive male patients, 6 of whom had mutations of BRCA2, were also examined for steroid receptors. Estrogen receptor (ER) and progesterone receptor (PgR) analyses were performed with radioligand or enzyme ***immunoassay*** techniques on tumor cytosol preparations. ***Germline*** mutation screening and detection were performed using the protein truncation test, single strand conformation polymorphism, and direct sequencing on DNA from normal tissue. RESULTS. The BRCA1-related tumors expressed significantly lower levels of ER than tumors from the other hereditary groups. The PgR levels were significantly lower in the BRCA1- related cases than in the hereditary cases not related to BRCA1 or BRCA2, but not significantly lower than in the BRCA2-related cases. Fourteen of 32 (44%) of the hereditary tumors not related to BRCA1 or BRCA2 had PgR levels exceeding 100 fmol/mg of protein. The tumors from male patients with BRCA2- related disease did not have receptor levels that differed from those in non-BRCA2-related tumors. CONCLUSIONS. BRCA1- and BRCA2-related ***breast*** tumors were distinct in their expression of steroid receptors. Moreover, a subgroup of tumors not related to BRCA1 or BRCA2 manifested a strongly positive PgR phenotype rarely seen in BRCA1- and BRCA2-related tumors. These characteristics may be of relevance to the treatment and follow-up of high risk individuals in these families and may help identify a homogenous category of hereditary ***breast*** carcinomas not related to BRCA1 or BRCA2 in which new ***susceptibility*** genes may be sought.

L65 ANSWER 24 OF 52 MEDLINE

DUPLICATE 12

ACCESSION NUMBER: 1998262367 MEDLINE

DOCUMENT NUMBER: 98262367 PubMed ID: 9599633

TITLE: [Should we screen for ***prostate*** ***cancer*** ?].

Faut-il dépister le ***cancer*** de ***prostate*** ?.

AUTHOR: Mangin P; Cormier L; Valeri A

CORPORATE SOURCE: Service d'Urologie, CHU Nancy-Brabois.

SOURCE: ANNALES D UROLOGIE, (1998) 32 (2) 63-7.

Journal code: 6AD; 0212342. ISSN: 0003-4401.

PUB. COUNTRY: France

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: French

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199806

ENTRY DATE: Entered STN: 19980618

Last Updated on STN: 19980618

Entered Medline: 19980611

AB The controversy concerning the justification for ***prostatic*** ***cancer*** screening is now about ten years old. It is the consequence of several convergent phenomena: the routine use of new ***diagnostic*** tools such as ***prostate*** specific antigen, ageing of ***Western*** populations, increased life expectancy and finally public health economic aspects. Is screening justified before the age of 50 years? The answer is no, except in high-risk families with several cases of ***prostatic*** ***cancer***, in which screening should be started at the age of 40 years. Is screening justified after the age of 70 years? The answer is no, except in men between 70 and 75 years whose general state and physiological age suggest that they have a life

expectancy exceeding ten years. Is screening justified between 50 and 70 years? There is no global "medico-economic" answer to this question, as medical truth, i.e. the individual's interests, appears to be diametrically opposed to economic truth, i.e. the community's interests, due to the high cost of screening. How can screening be envisaged for the future? In families with no particular risk, screening should be clinical, but will probably start earlier and will continue later, because of the improvement of ***diagnostic*** tools and prolongation of life expectancy. In high-risk families, the development of genetic tests will be able to determine whether or not a man has ***inherited*** predisposition genes. If he has ***inherited*** these genes, he will then be submitted to particularly early, meticulous and repeated screening.

L65 ANSWER 25 OF 52 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:684517 CAPLUS

DOCUMENT NUMBER: 128:970

TITLE: ***Diagnosis*** and prognosis of ***cancer***
based on detection of mutations and polymorphisms in
the human tumor suppressor gene pRb2/p130

INVENTOR(S): Giordano, Antonio; Baldi, Alfonso

PATENT ASSIGNEE(S): Thomas Jefferson University, USA

SOURCE: PCT Int. Appl., 169 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9738125	A1	19971016	WO 1997-US5598	19970403
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
CA 2250854	AA	19971016	CA 1997-2250854	19970403
AU 9724389	A1	19971029	AU 1997-24389	19970403
EP 906448	A1	19990407	EP 1997-920115	19970403
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI			
JP 2000510330	T2	20000815	JP 1997-536340	19970403
PRIORITY APPLN. INFO.:			US 1996-14943	P 19960405
			US 1996-19372	P 19960605
			US 1996-20196	P 19960621
			US 1997-39532	P 19970303
			WO 1997-US5598	W 19970403

AB The invention provides ***diagnostic*** and prognostic methods which comprise detg. the level of expression of the tumor suppressor gene pRb2/p130. Because the relative level of pRb2/p130 expression correlates with the presence of ***cancer***, tumor grade, and patient prognosis, these methods may be used to detect ***cancer***, to make treatment decisions, to predict patient outcome, and to predict the risk of ***cancer*** in disease-free individuals. The invention further provides methods for the detection of mutations and polymorphisms in the

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pRb2/p130 gene, which may be used to characterize genetic events assocd. with tumor formation, to trace the parental origin of mutations, to identify carriers of ***germline*** mutations, and to identify individuals with a predisposition to ***cancer***. The human pRb2/p130 gene and its promoter has been cloned and sequenced, and shown to contain 22 exons and 21 introns, spanning >50 kb of genomic DNA. The location and size of each exon and intron of pRb2/p130, as well as the nucleotide sequences at the exon-intron junctions, are provided. PCR primers are provided for amplification of each of the gene exons and the promoter region, which can be used for the detection of mutations.

L65 ANSWER 26 OF 52 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:805556 CAPLUS

DOCUMENT NUMBER: 128:58317

TITLE: In vivo mutations and polymorphisms in the 17q-linked ***breast*** and ***ovarian*** ***cancer*** ***susceptibility*** gene BRCA1

INVENTOR(S): Shattuck-Eidens, Donna M.; Simard, Jacques; Durocher, Francine; Emi, Mitsuuru; Nakamura, Yusuke

PATENT ASSIGNEE(S): Myriad Genetics, Inc., USA; Centre de Recherche du Chul; Cancer Institute

SOURCE: U.S., 101 pp. Cont.-in-part of U.S. Ser. No. 409,305, abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5693473	A	19971202	US 1995-480784	19950607
CA 2196797	AA	19960222	CA 1995-2196797	19950811
WO 9605306	A2	19960222	WO 1995-US10202	19950811
WO 9605306	A3	19960314		
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9533212	A1	19960307	AU 1995-33212	19950811
AU 686004	B2	19980129		
EP 705903	A1	19960410	EP 1995-305605	19950811
EP 705903	B1	20010523		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1169753	A	19980107	CN 1995-195259	19950811
CN 1172502	A	19980204	CN 1995-195413	19950811
FI 9700513	A	19970407	FI 1997-513	19970207
NO 9700624	A	19970414	NO 1997-624	19970211
PRIORITY APPLN. INFO.:				
			US 1994-289221	B2 19940812
			US 1994-300266	B2 19940902
			US 1994-308104	B2 19940909
			US 1994-348824	B2 19941129
			US 1995-409305	B2 19950324
			US 1995-480784	A 19950607
			US 1995-483553	A 19950607
			WO 1995-US10202	W 19950811

AB The present invention relates to methods and materials used to isolate and detect a human ***breast*** and ***ovarian*** ***cancer***

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predisposing gene (BRCA1), and some mutant alleles of which cause
susceptibility to ***cancer***, in particular ***breast***
and ***ovarian*** ***cancer***. More specifically, the invention
relates to ***germline*** mutations in the BRCA1 gene and their use in
the ***diagnosis*** of predisposition to ***breast*** and
ovarian ***cancer***. The present invention further relates
to somatic mutations in the BRCA1 gene in human ***breast*** and
ovarian ***cancer*** and their use in the ***diagnosis***
and prognosis of human ***breast*** and ***ovarian***
cancer. The invention also relates to the therapy of human
cancers which have a mutation in the BRCA1 gene, including gene therapy,
protein replacement therapy and protein mimetics. The invention further
relates to the screening of drugs for ***cancer*** therapy. Finally,
the invention relates to the screening of the BRCA1 gene for mutations,
which are useful for ***diagnosing*** the predisposition to
breast and ***ovarian*** ***cancer***. The human gene
BRCA1 involved in predisposition to ***breast*** and ***ovarian***
cancer is cloned and characterized and somatic and
germline mutations that may play a role in carcinogenesis are
characterized. Methods for detection of mutation in the gene are also
described. Characterization of mutations in BRCA1 assocd. with specific
human cancers may allow for therapy including gene therapy, protein
replacement therapy and protein mimetics (no data).

L65 ANSWER 27 OF 52 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:344787 CAPLUS

DOCUMENT NUMBER: 126:326450

TITLE: ***Germline*** mutations in the Multiple Tumor
Suppressor gene MTS and ***cancer***
diagnosis, prognosis, and therapy

INVENTOR(S): Skolnick, Mark H.; Cannon-Albright, Lisa A.; Kamb,
Alexander

PATENT ASSIGNEE(S): University of Utah Research Foundation, USA; Myriad
Genetics, Inc.

SOURCE: U.S., 72 pp. Cont.-in-part of U.S. Ser. No. 251,938,
abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5624819	A	19970429	US 1995-474177	19950607
CA 2162150	AA	19950928	CA 1995-2162150	19950317
CN 1128049	A	19960731	CN 1995-190374	19950317

PRIORITY APPLN. INFO.:

US 1994-214582	B2	19940318
US 1994-215086	B2	19940318
US 1994-215087	B2	19940318
US 1994-227369	B2	19940414
US 1994-251938	B2	19940601

AB The present invention relates to somatic mutations in the Multiple Tumor
Suppressor (MTS) gene in human cancers and their use in the
diagnosis and prognosis of human ***cancer***. The invention
further relates to ***germline*** mutations in the MTS gene and their
use in the ***diagnosis*** of predisposition to ***melanoma***,
leukemia, astrocytoma, glioblastoma, lymphoma, glioma, Hodgkin's lymphoma,
CLL, and cancers of the ***pancreas***, ***breast***, thyroid,

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ovary , uterus, testis, kidney, stomach and rectum. The invention also relates to the therapy of human cancers which have a mutation in the MTS gene, including gene therapy, protein replacement therapy and protein mimetics. Finally, the invention relates to the screening of drugs for ***cancer*** therapy.

L65 ANSWER 28 OF 52 MEDLINE

ACCESSION NUMBER: 97303215 MEDLINE
DOCUMENT NUMBER: 97303215 PubMed ID: 9159158
TITLE: Human BRCA1 inhibits growth in yeast: potential use in
diagnostic testing.
AUTHOR: Humphrey J S; Salim A; Erdos M R; Collins F S; Brody L C;
Klausner R D
CORPORATE SOURCE: Medicine Branch, National Cancer Institute, National
Institutes of Health, Bethesda, MD 20892, USA..
jshumphr@helix.nih.gov
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE
UNITED STATES OF AMERICA, (1997 May 27) 94 (11) 5820-5.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 19970630
Entered Medline: 19970619

AB ***Germline*** -inactivating mutations of BRCA1 result in a hereditary predisposition to ***breast*** and ***ovarian*** ***cancer*** . Truncating mutations of BRCA1 predispose to ***cancer*** and can be ascertained by protein truncation testing or sequencing. However, ***cancer*** -predisposing missense mutations of BRCA1 are difficult to distinguish from polymorphisms by genetic testing methods currently used. Here we show that expression of BRCA1 or BRCA1 fused to a GAL4 activation domain in *Saccharomyces cerevisiae* inhibits growth, resulting in small colonies easily distinguishable from vector-transformed controls. The growth inhibitory effect can be localized to sequences encoding the recently described BRCA1 C-terminal domains. Growth suppression by a BRCA1 fusion protein is not influenced by introduction of neutral polymorphisms but is diminished or abolished by frameshift, nonsense, or disease-associated missense mutations located in the C-terminal 305 amino acids of BRCA1. These observations may permit the functional significance of many BRCA1 sequence changes to be assessed in yeast. Additionally, the correlation of growth suppression with wild-type forms of BRCA1 suggests that the assay may be capable of detecting functionally conserved interactions between the evolutionarily conserved BRCA1 C-terminal domains and cellular elements found in both human and yeast cells.

L65 ANSWER 29 OF 52 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1996:748614 CAPLUS
DOCUMENT NUMBER: 126:15536
TITLE: Tumorigenic BRCA1 mutations as genetic markers for
breast and ***ovarian*** ***cancer***
INVENTOR(S): King, Mary-Claire; Friedman, Lori; Ostermeyer, Beth;
Rowel, Sarah; Lynch, Eric; Szabo, Csilla; Lee, Ming
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

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LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9633271	A2	19961024	WO 1996-US5621	19960419
WO 9633271	A3	19970320		
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML				
US 5622829	A	19970422	US 1995-425061	19950419
CA 2217668	AA	19961024	CA 1996-2217668	19960419
AU 9655668	A1	19961107	AU 1996-55668	19960419
AU 698800	B2	19981105		
EP 821733	A2	19980204	EP 1996-913045	19960419
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11503915	T2	19990406	JP 1996-531995	19960419
US 5821328	A	19981013	US 1997-825886	19970402
PRIORITY APPLN. INFO.:				
			US 1995-425061	19950419
			US 1993-163959	19931208
			US 1994-232535	19940418
			US 1994-326983	19941020
			WO 1996-US5621	19960419
AB Twelve BRCA1 alleles and their translation products are provided that are assocd. with ***breast***, ***ovarian***, and ***prostatic*** cancers. The tumorigenic BRCA1 cDNA alleles were isolated and characterized by positional cloning and screening of cDNA libraries for mutations. These 12 markers can be used to ***diagnose*** ***inherited*** ***susceptibility*** to ***cancer*** by (1) nucleic acid-based methods such as PCR primers or hybridization probes, and (2) contacting the translation products with specific reagents such as antibodies.				

L65 ANSWER 30 OF 52 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1996:332754 CAPLUS

DOCUMENT NUMBER: 125:2991

TITLE: In vivo mutations and polymorphisms in the 17q-linked ***breast*** and ***ovarian*** ***cancer*** ***susceptibility*** gene BRCA1

INVENTOR(S): Shattuck-Eidens, Donna M.; Simard, Jacques; Emi, Mitsuru; Nakamura, Yusuke; Durocher, Francine

PATENT ASSIGNEE(S): Myriad Genetics, Inc., USA; Centre De Recherche Du Chul; Cancer Institute

SOURCE: PCT Int. Appl., 208 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9605306	A2	19960222	WO 1995-US10202	19950811
WO 9605306	A3	19960314		

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W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG,
 KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO,
 RU, SD, SI, SK, TJ, TT, UA, UZ, VN
 RW: KE, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE,
 SN, TD, TG

US 5693473	A	19971202	US 1995-480784	19950607
US 5709999	A	19980120	US 1995-483553	19950607
AU 9533212	A1	19960307	AU 1995-33212	19950811
AU 686004	B2	19980129		
CN 1169753	A	19980107	CN 1995-195259	19950811
FI 9700513	A	19970407	FI 1997-513	19970207
NO 9700624	A	19970414	NO 1997-624	19970211

PRIORITY APPLN. INFO.:

US 1994-289221	A	19940812
US 1994-300266	A	19940902
US 1994-308104	A	19940916
US 1994-348824	A	19941129
US 1995-409305	A	19950324
US 1995-480784	A	19950607
US 1995-483553	A	19950607
WO 1995-US10202	W	19950811

AB The human gene BRCA1 involved in predisposition to ***breast*** and
 ovarian ***cancer*** is cloned and characterized and somatic
 and ***germline*** mutations that may play a role in carcinogenesis
 are characterized. Methods for detection of mutation in the gene are also
 described. Characterization of mutations in BRCA1 assocd. with specific
 human cancers may allow for therapy including gene therapy, protein
 replacement therapy and protein mimetics (no data). The invention further
 relates to the screening of drugs for ***cancer*** therapy. Finally,
 the invention relates to the screening of the BRCA1 gene for mutations,
 which are useful for ***diagnosing*** the predisposition to
 breast and ***ovarian*** ***cancer***.

L65 ANSWER 31 OF 52 MEDLINE

ACCESSION NUMBER: 96387143 MEDLINE
 DOCUMENT NUMBER: 96387143 PubMed ID: 8848675
 TITLE: [Hereditary nonpolyposis colorectal cancers].
 Le ***cancer*** colorectal hereditaire non polyposique.
 AUTHOR: Caplin S; Constanda M T; Givel J C
 CORPORATE SOURCE: Service de chirurgie, CHUV, Lausanne.
 SOURCE: SCHWEIZERISCHE RUNDSCHAU FUR MEDIZIN PRAXIS, (1996 Aug 27)
 85 (35) 1041-5. Ref: 68
 Journal code: SRM; 8403202. ISSN: 1013-2058.
 PUB. COUNTRY: Switzerland
 Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: French
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199610
 ENTRY DATE: Entered STN: 19961106
 Last Updated on STN: 19961106
 Entered Medline: 19961024

AB Hereditary non-polyposis colorectal ***cancer*** (HNPCC) is an
 autosomal, dominantly ***inherited*** disease leading to a marked
 increase in ***cancer*** ***susceptibility***, notably colorectal
 cancer, affecting up to one in 400 individuals in the
 Western world. Four genes responsible for the majority of cases
 have been identified. Colorectal ***cancer*** in affected people tends
 to be right sided, occur at an earlier age, and there is a propensity for

synchronous or metachronous lesions. Extra-colonic tumours may occur with an elevated frequency, most importantly ***cancer*** of the endometrium, but also stomach, hepatobiliary system, small bowel, proximal ureter and ***renal*** pelvis, and ***ovary***. On account of these features, management guidelines for members of HNPCC kindreds require modification from those generally advised for patients with sporadic tumours. The cardinal feature for the identification of affected families is the family history. All clinicians have a duty to identify such patients under their care as appropriate screening and surgery should lead to an improved prognosis for such patients and their families.

L65 ANSWER 32 OF 52 MEDLINE

DUPLICATE 13

ACCESSION NUMBER: 96362567 MEDLINE

DOCUMENT NUMBER: 96362567 PubMed ID: 8720282

TITLE: Endogenous and exogenous factors in carcinogenesis: limits to ***cancer*** prevention.

AUTHOR: Lutz W K; Fekete T

CORPORATE SOURCE: Department of Toxicology, University of Wurzburg, Germany.

SOURCE: INTERNATIONAL ARCHIVES OF OCCUPATIONAL AND ENVIRONMENTAL HEALTH, (1996) 68 (2) 120-5.

Journal code: GPN; 7512134. ISSN: 0340-0131.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199610

ENTRY DATE: Entered STN: 19961106

Last Updated on STN: 19961106

Entered Medline: 19961018

AB Organ-specific ***cancer*** incidence rates can vary dramatically between low- and high-incidence areas. Such differences are due to (1) ***heritable*** ***susceptibility*** determinants, (2) risk factors associated with the environmental and local living conditions (e.g., viruses, pollution), and (3) personal life-style factors. For organs showing large differences between ***cancer*** registries, exogenous factors might be most important, while for organs showing only small differences, endogenous and unavoidable factors are expected to be more important. In this paper, a working hypothesis based on descriptive ***cancer*** epidemiology is presented to estimate, in a quantitative manner, the unavoidable contribution to the process of carcinogenesis and to discuss limitations to individual ***cancer*** prevention. Cumulative ***cancer*** incidence rates for a 75-year period of life (CR74, in percent) were taken from IARC Scientific Publication No. 120 (1992). For each organ, values were ranked in ascending order, and the ratio between high-rate and low-rate registries (90th percentile/10th percentile) was determined. This measure of variability among registries differed strongly between organs. Largest ratios were seen for organs with well-known exogenous risk factors, such as pharynx, lip, tongue, mouth, liver, esophagus, and ***melanoma*** in males, and lung, esophagus, gallbladder, liver, and bladder in females. Small ratios were seen for rectum, brain, colon, and Hodgkin's disease in males, and ***breast***, rectum, ***ovary***, brain, and colon in females. It is concluded that the process of carcinogenesis in the latter organs has a stronger endogenous/unavoidable component, for some tissues possibly of hormonal type. A fictitious population was composed where, for each organ, the minimum reported ***cancer*** rate was taken. When based on all ***cancer*** registries world-wide, CR74 sums over all sites of 2.0% and 2.3% resulted in males and females, respectively. When only Central/ ***Western*** European countries were included in the analysis in order

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to reduce differences in risk factors nos. 1 and 2, the sum of the minimum values was 10.4% and 8.7%. After correction of the data for smoking, 'minimum' ***cancer*** incidence rates in males and females were estimated to be 7.6% and 6.8%. Based on a median ***cancer*** incidence rate for nonsmoking males in Europe of about 21%, therefore, individual preventive measures taken by a nonsmoker can reduce the ***cancer*** risk, on average, 'only' by a factor of about 3. A considerable fraction of cases thus appears to be hardly avoidable.

L65 ANSWER 33 OF 52 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1995:988054 CAPLUS

DOCUMENT NUMBER: 124:23302

TITLE: ***Germline*** mutations in the Multiple Tumor Suppressor (MTS) gene and method for detecting predisposition to ***cancer*** at the MTS gene
INVENTOR(S): Skolnick, Mark H.; Cannon-Albright, Lisa A.; Kamb, Alexander

PATENT ASSIGNEE(S): University of Utah Research Foundation, USA; Myraid Genetics, Inc.

SOURCE: PCT Int. Appl., 148 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9525813	A1	19950928	WO 1995-US3537	19950317
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TT, UA, UG, US, UZ, VN				
RW: KE, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2162150	AA	19950928	CA 1995-2162150	19950317
AU 9523789	A1	19951009	AU 1995-23789	19950317
AU 685627	B2	19980122		
EP 702730	A1	19960327	EP 1995-916914	19950317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1128049	A	19960731	CN 1995-190374	19950317
JP 08510391	T2	19961105	JP 1995-524780	19950317
NO 9504495	A	19960117	NO 1995-4495	19951108
FI 9505416	A	19960109	FI 1995-5416	19951110
US 5989815	A	19991123	US 1997-848251	19970429
PRIORITY APPLN. INFO.:			US 1994-214582	A 19940318
			US 1994-215086	A 19940318
			US 1994-215087	A 19940318
			US 1994-227369	A 19940414
			US 1994-251938	A 19940601
			WO 1995-US3537	W 19950317
			US 1995-474083	B1 19950607

AB The present invention relates to somatic mutations in the Multiple Tumor Suppressor (MTS) gene in human cancers and their use in the ***diagnosis*** and prognosis of human ***cancer***. The invention further relates to ***germline*** mutations in the MTS gene and their use in the ***diagnosis*** of predisposition to ***melanoma***, leukemia, astrocytoma, glioblastoma, lymphoma, glioma, Hodgkin's lymphoma, CLL, and cancers of the ***pancreas***, ***breast***, thyroid, ***ovary***, uterus, testis, kidney, stomach and rectum. The invention

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also relates to the therapy of human cancers which have a mutation in the MTS gene, including gene therapy, protein replacement therapy and protein mimetics. Finally, the invention relates to the screening of drugs for ***cancer*** therapy.

L65 ANSWER 34 OF 52 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 95354141 MEDLINE
DOCUMENT NUMBER: 95354141 PubMed ID: 7627958
TITLE: ***Germline*** mutation of BRCA1 in Japanese
breast ***cancer*** families.
AUTHOR: Inoue R; Fukutomi T; Ushijima T; Matsumoto Y; Sugimura T;
Nagao M
CORPORATE SOURCE: Carcinogenesis Division, National Cancer Center Research
Institute, Tokyo, Japan.
SOURCE: CANCER RESEARCH, (1995 Aug 15) 55 (16) 3521-4.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950921
Last Updated on STN: 19950921
Entered Medline: 19950907
AB We analyzed ***germline*** mutations of the BRCA1 gene in 18 Japanese
breast ***cancer*** families and two Japanese ***breast***
- ***ovarian*** ***cancer*** families. In two site-specific
breast ***cancer*** families, the same mutation was detected;
a nonsense mutation at codon 63 encoding a truncated small protein. It was
demonstrated that the mutant allele cosegregated with ***breast***
cancer patients within a family and was absent in healthy
Japanese, suggesting a ***breast*** ***cancer*** -predisposing
allele. The average age at ***diagnosis*** was 44 and 55 years in each
family with BRCA1 mutation. No bilateral ***breast*** ***cancer***
patients were present in the BRCA1 mutation-positive families, although
five were present in the BRCA1-negative families. No ***germline***
mutations of BRCA1 were detected in the two ***breast*** -
ovarian ***cancer*** families examined in this study, although
BRCA1 mutation plays a major role in ***breast*** - ***ovarian***
cancer families in ***Western*** countries. Thus, the
proportion of families who ***inherit*** the mutated BRCA1 allele
seems to be small among Japanese ***breast*** ***cancer***
families and Japanese ***breast*** - ***ovarian*** ***cancer***
families.

L65 ANSWER 35 OF 52 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95176201 EMBASE
DOCUMENT NUMBER: 1995176201
TITLE: Gastroenterology and hepatology.
AUTHOR: Koff R.S.
CORPORATE SOURCE: MetroWest Medical Center, Framingham, MA, United States
SOURCE: Journal of the American Medical Association, (1995) 273/21
(1679-1680).
ISSN: 0098-7484 CODEN: JAMAAP
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
016 Cancer
022 Human Genetics

037 Drug Literature Index
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Development of colon ***cancer*** is now believed to result from a series of ***inherited*** or acquired mutations in DNA. - Convincing evidence that colonoscopic polypectomy prevents colorectal ***cancer*** is now available. - A consensus panel recommended that all patients with duodenal and gastric ulcers who are infected with H pylori on first presentation be treated with antimicrobial agents.

L65 ANSWER 36 OF 52 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 15

ACCESSION NUMBER: 95175121 EMBASE

DOCUMENT NUMBER: 1995175121

TITLE: Immunohistochemical detection of P53 protein is not associated with a poor prognosis in non-small-cell lung ***cancer***

AUTHOR: Passlick B.; Izbicki J.R.; Haussinger K.; Thetter O.; Pantel K.

CORPORATE SOURCE: Department of Surgery, Universitätskrankenhaus Eppendorf, Martinistr. 52, 20246 Hamburg, Germany

SOURCE: Journal of Thoracic and Cardiovascular Surgery, (1995) 109/6 (1205-1211).

ISSN: 0022-5223 CODEN: JTCSAQ

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 009 Surgery
015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Immunohistochemical detection of the p53 gene product by monoclonal antibodies has been shown to be associated with a poor clinical outcome in carcinomas of the ***breast*** and stomach. Because the prognostic relevance of p53 immunostaining in lung ***cancer*** is still under debate, we studied the expression pattern and clinical significance of such staining in 73 patients with operable non-small-cell lung ***cancer***. p53 expression was detected on frozen sections with the use of monoclonal ***antibody*** p1801, which recognizes both the wild-type and mutant gene product (alkaline phosphatase-anti-alkaline phosphatase method). A tumor was considered p53 positive if more than 1% of the tumor cells were stained. The p53 expression pattern was compared with clinicopathologic parameters, and analysis of follow-up, based on the data of 65 patients, was done by a log rank test (median observation time, 780 days). Nuclear p53 staining was detected in 33 of 73 non-small-cell lung cancers (45.2%). Comparison with clinicopathologic parameters demonstrated that the p53 protein was detected more frequently in younger patients (younger than 50 years, $p = 0.014$), whereas no correlation was found with sex, tumor differentiation, tumor histologic type, or TNM stage. Surprisingly, follow-up analysis revealed that p53 staining was associated with an increased rate of disease-free survival, especially in patients with early stage tumor disease ($p = 0.004$) and in male patients ($p = 0.023$). Counter to previous studies in other solid tumors, immunocytochemical detection of p53 expression does not predict a poor clinical outcome in non-small-cell lung ***cancer***. In early-stage lung ***cancer*** it might be associated with an improved disease-free survival, which suggests that the majority of the detected protein ***inherits*** the wild-type tumor suppressor function.

L65 ANSWER 37 OF 52 MEDLINE

ACCESSION NUMBER: 95326337 MEDLINE
 DOCUMENT NUMBER: 95326337 PubMed ID: 7541479
 TITLE: Usefulness of amylase isoenzyme determination for the
 diagnosis of ***pancreatic*** diseases.
 AUTHOR: Otsuki M
 CORPORATE SOURCE: Third Department of Internal Medicine, School of Medicine,
 University of Occupational and Environmental Health, Japan.
 SOURCE: NIPPON RINSHO. JAPANESE JOURNAL OF CLINICAL MEDICINE, (1995
 May) 53 (5) 1184-91. Ref: 23
 Journal code: KIM; 0420546. ISSN: 0047-1852.
 PUB. COUNTRY: Japan
 Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: Japanese
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199508
 ENTRY DATE: Entered STN: 19950822
 Last Updated on STN: 19960129
 Entered Medline: 19950807

AB Serum amylase shows the greatest increase among the various
 pancreatic enzymes that increase at the onset of acute
 pancreatitis. However, the ***diagnostic*** value of the total serum
 amylase activity has been questioned due to its lack of specificity. To
 differentiate hyperamylasemia due to ***pancreatic*** disease from
 that due to other causes, the activity of ***pancreatic*** amylase
 should be determined by using a monoclonal ***antibody*** that
 specifically binds to ***pancreatic*** or salivary amylase, or by
 electrophoresis. The most useful and accurate method for distinguishing
 pancreatic from salivary-type hyperamylasemia is isoamylase
 analysis by electrophoresis. In patients with acute pancreatitis, increase
 of Amylase-1 and -2 is accompanied by the appearance of Amylase-4, a minor
 component of the ***pancreatic*** -type isoamylases, and by
 disappearance of the salivary-type isoenzymes, thereby leaving a pattern
 of the ***pancreatic*** isoenzymes alone. This pancreatitis pattern
 persists for about 10 days after the onset of illness. Therefore, if such
 a pattern is found in a patient with clinical findings suggesting acute
 pancreatitis despite a normal serum amylase level, the patient can be
 diagnosed as having acute pancreatitis or a recent attack of the
 disease. However, the existence of an ***inherited*** trait of the
 pancreatitis pattern in some healthy individuals must be borne in mind.
 Patients with recurrent chronic pancreatitis also show ***pancreatic***
 -type hyperamylasemia, whereas the ***pancreatic*** amylase activity
 decreases when ***pancreatic*** exocrine insufficiency progresses.
 Hyperamylasemia due to elevated salivary amylase activity is also common
 in patients with diabetic ketosis or malignancies such as lung
 cancer (adenocarcinoma). Hyperamylasemia is also found following
 various types of operation. In most cases, it is salivary-type
 hyperamylasemia. (ABSTRACT TRUNCATED AT 250 WORDS)

L65 ANSWER 38 OF 52 MEDLINE

DUPLICATE 16

ACCESSION NUMBER: 96112016 MEDLINE
 DOCUMENT NUMBER: 96112016 PubMed ID: 8524414
 TITLE: Identification of the ***breast*** ***cancer***
 susceptibility gene BRCA2.
 COMMENT: Comment in: Nature. 1995 Dec 21-28;378(6559):762-3
 Erratum in: Nature 1996 Feb 22;379(6567):749
 AUTHOR: Wooster R; Bignell G; Lancaster J; Swift S; Seal S; Mangion

09480389a

CORPORATE SOURCE: J; Collins N; Gregory S; Gumbs C; Micklem G
Section of Molecular Carcinogenesis, Haddow Laboratories,
Sutton Surrey, UK.
SOURCE: NATURE, (1995 Dec 21-28) 378 (6559) 789-92.
Journal code: NSC; 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-X95151; GENBANK-X95152; GENBANK-X95153;
GENBANK-X95154; GENBANK-X95155; GENBANK-X95156;
GENBANK-X95157; GENBANK-X95158; GENBANK-X95159;
GENBANK-X95160; GENBANK-X95161; GENBANK-X95162;
GENBANK-X95163; GENBANK-X95164; GENBANK-X95165;
GENBANK-X95166; GENBANK-X95167; GENBANK-X95168;
GENBANK-X95169; GENBANK-X95170; GENBANK-X95171;
GENBANK-X95172; GENBANK-X95173; GENBANK-X95174;
GENBANK-X95175; GENBANK-X95176; GENBANK-X95177
ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 19960219
Last Updated on STN: 19980206
Entered Medline: 19960124

AB In ***Western*** Europe and the United States approximately 1 in 12
women develop ***breast*** ***cancer***. A small proportion of
breast ***cancer*** cases, in particular those arising at a
young age, are attributable to a highly penetrant, autosomal dominant
predisposition to the disease. The ***breast*** ***cancer***
susceptibility gene, BRCA2, was recently localized to chromosome
13q12-q13. Here we report the identification of a gene in which we have
detected six different ***germline*** mutations in ***breast***
cancer families that are likely to be due to BRCA2. Each mutation
causes serious disruption to the open reading frame of the transcriptional
unit. The results indicate that this is the BRCA2 gene.

L65 ANSWER 39 OF 52 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 95345024 EMBASE
DOCUMENT NUMBER: 1995345024
TITLE: Medullary thyroid carcinoma: Recent advances and management
update.
AUTHOR: Marsh D.J.; Learoyd D.L.; Robinson B.G.
CORPORATE SOURCE: Molecular Genetics Unit, Kolling Inst. of Medical Research,
Royal North Shore Hospital, St Leonards, NSW 2065, Australia
SOURCE: Thyroid, (1995) 5/5 (407-424).
ISSN: 1050-7256 CODEN: THYRER
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
016 Cancer
022 Human Genetics
023 Nuclear Medicine
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Medullary thyroid carcinoma (MTC) is a malignancy of the thyroid C-cells
that comprises 5-10% of all thyroid cancers. MTC occurs in both sporadic
and familial forms, the latter making up 25% of all MTCs and being
comprised of three distinct syndromes - multiple endocrine neoplasia type
2A (MEN 2A), multiple endocrine neoplasia type 2B (MEN 2B), and familial
medullary thyroid carcinoma (FMTC). To date, screening for MTC has been

performed using the pentagastrin stimulation test, which is a provocative test for calcitonin release. ***Germline*** mutations in the RET protooncogene have been identified in families manifesting these syndromes and genetic screening of individuals at risk of one of these syndromes has become integral to their clinical management. The majority of the mutations associated with MEN 2A and FMTC are tightly clustered in a cysteine-rich region of the RET receptor. A single mutation associated with MEN 2B is in the tyrosine kinase domain of the RET receptor. Somatic mutations have been identified in the tumor tissue of individuals with sporadic MTC and may prove to be helpful markers in discerning the hereditary or sporadic nature of the MTC. There is general agreement that the primary operation for MTC should include total thyroidectomy and central neck lymph node clearance. The role of microdissection for recurrent disease awaits longitudinal evaluation. External radiotherapy, radionuclide therapy, and chemotherapy may have a role in palliation, but have not been proven to have a curative value. Prognostic factors are discussed.

L65 ANSWER 40 OF 52 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1995:364732 BIOSIS

DOCUMENT NUMBER: PREV199598379032

TITLE: A DNA probe study on the origin of the ***cancer*** recognition, immunodefense suppression and serine protease protection peptide.

AUTHOR(S): Cercek, Lea; Siaw, Martin; Cercek, Bibijana (1); Cercek, Boris

CORPORATE SOURCE: (1) Beckman Inc., DSG/ATC, D/7799, W-355, 200 South Kraemer Blvd., Brea, CA 92621 USA

SOURCE: Cancer Detection and Prevention, (1995) Vol. 19, No. 4, pp. 325-330.

ISSN: 0361-090X.

DOCUMENT TYPE: Article

LANGUAGE: English

AB A quantitative "two DNA probe" dot blot hybridization assay, using chemiluminescence detection, was used to distinguish between the mRNA and DNA coding for the ***cancer*** recognition, immunodefense suppression, and serine protease protection (CRISPP) peptide, and the partially homologous C-terminal end sequence of the alpha-1-PI. In ***cancer*** cells, there is up to 2.4 times more mRNA and up to 6.3 times more DNA coding for the CRISPP peptide than for the homologous alpha-1-PI in their normal cell counterparts. This corroborates results of the "two ***antibody*** " ***immunoassay*** , which showed that ***cancer*** cells produce the CRISPP peptide in addition to alpha-1-PI molecules. The amplified transcription of the CRISPP peptide DNA could be the result of derepression and/or translocation of an ***inherited*** , or acquired, ***heritable*** damage to the DNA in the exon V of the alpha-1-PI gene. Expression of the CRISPP peptide mRNA and DNA in SV40 transformed cells could indicate that a viral transduction causes the amplified transcription of a mutated exon V of the alpha-1-PI gene and/or loss of a specific suppressor gene. The CRISPP peptide with its multiple, ***cancer*** -promoting biological effects may qualify as a product of a novel, as yet unidentified, oncogene. The detection of the CRISPP peptide DNA regions, using the two DNA probe, or some other suitable methods, might be a useful adjunct in ***cancer*** ***diagnosis*** of biopsies and/or in predictive ***diagnosis*** of familial cancers.

L65 ANSWER 41 OF 52 MEDLINE

DUPLICATE 17

ACCESSION NUMBER: 95069913 MEDLINE

DOCUMENT NUMBER: 95069913 PubMed ID: 7979195

09480389a

TITLE: What is hereditary nonpolyposis colorectal ***cancer***
(HNPCC).
AUTHOR: Vasen H F
CORPORATE SOURCE: The Netherlands Foundation for the Detection of Hereditary
Tumours, Utrecht/Leiden.
SOURCE: ANTICANCER RESEARCH, (1994 Jul-Aug) 14 (4B) 1613-5. Ref:
29
Journal code: 59L; 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19950110
Entered Medline: 19941215

AB Hereditary nonpolyposis colorectal ***cancer*** (HNPCC) is an
autosomal dominantly ***inherited*** disease associated with a marked
increase in ***cancer*** ***susceptibility***, especially
cancer of the colorectum. It is one of the most common
cancer predisposing syndromes affecting as many as one in 400
individuals in the ***Western*** World. Two (mismatch repair) genes
(hMSH2 on chromosome 2p and hMLH1 on chromosome 3p) have recently been
identified which appear to be involved in the development of
cancer in most of the HNPCC families. Colorectal ***cancer***
in HNPCC differs from sporadic colorectal ***cancer*** by an early age
of onset, a proclivity for the proximal colon, and an excess of
synchronous and metachronous colorectal cancers. A variety of extracolonic
tumors may be encountered in HNPCC, including cancers of the endometrium,
stomach, small bowel, urinary tract (***renal*** pelvis and ureter),
biliary system and ***ovary***. The ***diagnosis*** HNPCC
is currently based upon the combined patient and family data. Future
identification of HNPCC will be facilitated by the introduction of genetic
markers. Identification of HNPCC families is extremely important, because
periodic examination may prevent development of disease and death from
cancer.

L65 ANSWER 42 OF 52 MEDLINE

DUPLICATE 18

ACCESSION NUMBER: 95155157 MEDLINE
DOCUMENT NUMBER: 95155157 PubMed ID: 7852187
TITLE: Linkage analysis of BRCA1 in Japanese ***breast***
cancer families.
AUTHOR: Inoue R; Fukutomi T; Ushijima T; Matsumoto Y; Sugimura T;
Nagao M
CORPORATE SOURCE: Carcinogenesis Division, National Cancer Center Research
Institute, Tokyo.
SOURCE: JAPANESE JOURNAL OF CANCER RESEARCH, (1994 Dec) 85 (12)
1233-9.
Journal code: HBA; 8509412. ISSN: 0910-5050.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950322
Last Updated on STN: 19950322
Entered Medline: 19950316

09480389a

AB We examined the involvement of BRCA1, which plays a major role in
Western ***breast*** ***cancer*** families, in Japanese
breast ***cancer*** families. Eleven families, in which at
least three individuals within third degree relatives were affected by
breast ***cancer***, were collected. Five of them were
early-onset ***breast*** ***cancer*** families, in which the
average age at ***diagnosis*** was less than 45 years, and the other
six were late-onset families. ***Ovarian*** ***cancer*** was
observed in one patient in the early-onset families. Using seven
polymorphic markers on chromosome 17q21, D17S250, ERBB2, THRA1, D17S579,
D17S588, GIP and NME1, linkage to BRCA1 was analyzed. Linkage was not
detected in any single family. Assuming homogeneity in an
inherited component that confines the ***susceptibility*** to
breast ***cancer*** in all families, we summed the LOD scores
of all families. The cumulative LOD score obtained was -1.86 for D17S588
at $\theta = 0.001$, indicating no linkage with BRCA1. Since the proportion
of families linked to BRCA1 is larger in ***Western*** early-onset
breast ***cancer*** families than in late-onset ones, we also
summed the LOD scores of five early-onset families. However, again a
negative LOD score was obtained. These results suggest that BRCA1 is not a
major ***breast*** ***cancer*** ***susceptibility*** gene in
Japanese familial ***breast*** ***cancer***.

L65 ANSWER 43 OF 52 MEDLINE

DUPLICATE 19

ACCESSION NUMBER: 94257441 MEDLINE
DOCUMENT NUMBER: 94257441 PubMed ID: 8198980
TITLE: The relationship between serum p53 autoantibodies and
characteristics of human ***breast*** ***cancer***.
AUTHOR: Mudenda B; Green J A; Green B; Jenkins J R; Robertson L;
Tarunina M; Leinster S J
CORPORATE SOURCE: Department of Surgery, Royal Liverpool University Hospital,
UK.
SOURCE: BRITISH JOURNAL OF CANCER, (1994 Jun) 69 (6) 1115-9.
Journal code: AV4; 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940714
Last Updated on STN: 19980206
Entered Medline: 19940707

AB Sera from 182 newly ***diagnosed*** ***breast*** ***cancer***
patients were assayed for antibodies to p53 using an enzyme-linked
immunosorbent assay (***ELISA***) method, and antibodies were detected
in 48 (26%) compared with 1 out of 76 (1.3%) normal control volunteers (P
= 0.0001). In ***breast*** ***cancer*** patients, autoantibodies
were found in all stages of disease progression: carcinoma in situ,
primary invasive ***breast*** ***cancer*** and in metastatic
disease. In the subset of patients in whom sequential sera were assessed
over a 6 month period, changes in the p53 ***antibody*** titres were
observed. The presence of antibodies to p53 correlated positively with
high histological grade (P = 0.0012) and a history of second primary
cancer (six positive out of eight cases). The incidence of
autoantibodies was lower in those patients with a first-degree relative
with ***breast*** ***cancer*** (P = 0.046). Out of 68 patients,
there was a significant correlation between positive p53 autoantibody
status and the detection of p53 protein in the tissue sections by
immunocytochemistry (P = 0.002). In the seronegative patients, positive

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p53 tumour staining was strongly associated with a family history of
breast ***cancer*** (P = 0.009). The p53 protein overexpressed
in ***heritable*** ***breast*** cancers may therefore be less
immunogenic. The presence of p53 autoantibodies provides important
additional information to immunochemistry and may identify patients with
aggressive histological types of ***breast*** ***cancer***.

L65 ANSWER 44 OF 52 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 94198244 EMBASE

DOCUMENT NUMBER: 1994198244

TITLE: Tumor markers for ***breast*** ***cancer*** :
Current utilities and future prospects.

AUTHOR: Hayes D.F.

CORPORATE SOURCE: Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA
02115, United States

SOURCE: Hematology/Oncology Clinics of North America, (1994) 8/3
(485-506).

ISSN: 0889-8588 CODEN: HCNAEQ

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
006 Internal Medicine
016 Cancer
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Tumor-associated markers have potential utility in identification,
screening, prognosis, detection, or monitoring ***breast***
cancer. Of the available markers, those with the greatest promise
in 1994 include the yet-to-be-cloned BrCa1, the p53 tumor suppressor
gene, tissue-associated prognostic factors such as HER-2/neu, cathepsin-D,
and indicators of angiogenesis, and circulating tumor markers that provide
an indication of clinical course, such as CA15-3 and CEA. Unfortunately,
the precise clinical utilities of all of these markers remain imprecise.
It is especially important that the relative independence of the markers
in relation to other available markers be determined so as to avoid the
unnecessary cost and expense of redundancy. Moreover, it is important that
the clinician be aware of the limitations in both sensitivity and
specificity of each marker so as not to over- or underinterpret the
predictive value of any test. With these caveats in mind, judicious
application of ***germline***, tissue, and soluble tumor markers can
improve clinical care of patients at risk for and with ***breast***
cancer.

L65 ANSWER 45 OF 52 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 94008333 EMBASE

DOCUMENT NUMBER: 1994008333

TITLE: A review of the hypercoagulable state.

AUTHOR: Eby C.S.

CORPORATE SOURCE: Department of Pathology, St. Louis Univ. School of
Medicine, Vista Avenue at Grand Boulevard, St. Louis, MO
63110-0250, United States

SOURCE: Hematology/Oncology Clinics of North America, (1993) 7/6
(1121-1142).

ISSN: 0889-8588 CODEN: HCNAEQ

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery

09480389a

025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English
SUMMARY LANGUAGE: English

AB The hypercoagulable state refers to those factors, both acquired and congenital, that predispose an individual to thromboembolic events. In this article, the major acquired and ***inherited*** conditions associated with an increased risk for venous thromboembolic events are critically reviewed.

L65 ANSWER 46 OF 52 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 93289361 EMBASE

DOCUMENT NUMBER: 1993289361

TITLE: Epstein-Barr virus-associated T-cell lymphoma in a
renal transplant patient.

AUTHOR: Kumar S.; Kumar D.; Kingma D.W.; Jaffe E.S.

CORPORATE SOURCE: Division of Surgical Pathology, Department of Pathology,
University of Texas Medical Branch, Galveston, TX 77555,
United States

SOURCE: American Journal of Surgical Pathology, (1993) 17/10
(1046-1053).

ISSN: 0147-5185 CODEN: AJSPDX

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
016 Cancer
025 Hematology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Posttransplant lymphoproliferative disorders in organ allograft recipients are most commonly of B cell origin, whereas T cell lymphomas are rarely described. We report a case of T cell immunoblastic large cell lymphoma associated with Epstein-Barr virus (EBV) that occurred in a recipient of a cadaveric ***renal*** transplant 7 years posttransplantation. On paraffin immunophenotyping, none of the neoplastic cells stained with the T cell-associated markers used, but did show strong CD30 expression. Flow cytometric studies revealed a predominance of T cells without definite evidence of T cell neoplasia. Frozen section immunophenotyping studies revealed a T cell phenotype with aberrant expression, and genotypic studies demonstrated T cell receptor .beta. gene rearrangement with ***germline*** configuration of immunoglobulin heavy chain and .kappa. light chain genes, confirming a T lineage. EBV-encoded RNA transcripts were demonstrated within the neoplastic cells by in situ hybridization. Southern blot analysis using probes derived from the terminal repeat region of the virus detected a single restriction band indicating a clonal population. We believe this is the first case of a posttransplant T cell lymphoma in which the EBV genome has been demonstrated. This case also illustrates the pitfalls of paraffin immunophenotyping in the ***diagnosis*** of T cell lymphoma.

L65 ANSWER 47 OF 52 MEDLINE

ACCESSION NUMBER: 93051987 MEDLINE

DOCUMENT NUMBER: 93051987 PubMed ID: 1427599

TITLE: Biochemical study on steroid sulfatase and its clinical
application to the obstetrics and gynecology.

AUTHOR: Sugawara T

09480389a

CORPORATE SOURCE: Department of Obstetrics and Gynecology, Hokkaido University School of Medicine, Sapporo, Japan.
SOURCE: HOKKAIDO IGAKU ZASSHI. HOKKAIDO JOURNAL OF MEDICAL SCIENCE, (1992 Jul) 67 (4) 552-62.
Journal code: GA9; 17410290R. ISSN: 0367-6102.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19960129
Entered Medline: 19921217

AB Steroid sulfatase desulfates a number of 3 beta-hydroxysteroid sulfates, converting inactive steroid hormone to the active form. I have developed an enzyme-linked immunosorbent assay (***ELISA***) using polyclonal ***antibody*** against the sulfatase which was purified from human placenta to measure an amount of the enzyme protein in sera of ***gynecologic*** ***cancer*** patients. By this method, it was found that the serum steroid sulfatase level is significantly elevated in patients with ***endometrial*** carcinoma (p less than 0.05) and ***ovarian*** carcinoma (p less than 0.01) as compared to that of normal women. Steroid sulfatase deficiency, X-linked ichthyosis (XLI) is an ***inherited*** skin disorder. The sulfatase gene and the enzyme protein were examined in patients with XLI. When the first and last (exon 10) exons of the sulfatase gene were amplified by PCR using patients' genomic DNA as templates, no product was detected in all six cases examined. In addition, neither mRNA of the sulfatase nor the enzyme protein was detected in a patient with XLI. These observations suggest that most Japanese XLI patients are caused by an extensive deletion of the steroid sulfatase gene.

Q L65 ANSWER 48 OF 52 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1992:546601 CAPLUS
DOCUMENT NUMBER: 117:146601
TITLE: An immunochemical analysis of the human nuclear phosphoprotein p53. New monoclonal antibodies and epitope mapping using recombinant p53
AUTHOR(S): Vojtesek, B.; Bartek, J.; Midgley, C. A.; Lane, D. P.
CORPORATE SOURCE: Dep. Biochem., Univ. Dundee, Dundee, DD1 4HN, UK
SOURCE: J. Immunol. Methods (1992), 151(1-2), 237-44
CODEN: JIMMBG; ISSN: 0022-1759
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Somatic mutation of the p53 gene is a very frequent event in the development of human neoplasia, and germ line mutations in p53 are responsible for an ***inherited*** ***cancer*** ***susceptibility*** syndrome. Many of the mutations in p53 found in human tumors are point mutations that result in the substitution of a single amino acid in the protein. These point mutant proteins are much more stable than the normal protein and the mutant product accumulates to a high level which permits important information about p53 expression to be obtained by immunochem. anal. Using bacterial expression systems to produce fragments of human p53 we have isolated and characterized new monoclonal antibodies to p53. These antibodies are suitable for the measurement of p53 in ***ELISA***, immunoblotting, and immunopptn. analyses. They are esp. useful in immunohistochem. as they are able to react strongly with p53 in conventionally fixed and processed histol. sections.

L65 ANSWER 49 OF 52 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1989:104087 BIOSIS

DOCUMENT NUMBER: BR36:49503

TITLE: ***DIAGNOSTIC*** IMMUNOPATHOLOGY.

AUTHOR(S): COLVIN R B; BHAN A K; MCCLUSKEY R T

CORPORATE SOURCE: IMMUNOPATHOLOGY UNIT, DEP. PATHOLOGY, MASSACHUSETTS GENERAL HOSP., BOSTON, MASS.

SOURCE: COLVIN, R. B., A. K. BHAN AND R. T. MCCLUSKEY (ED.).
DIAGNOSTIC IMMUNOPATHOLOGY. XV+512P. RAVEN PRESS, LTD.: NEW YORK, NEW YORK, USA. ILLUS, (1988) 0 (0), XV+512P.
ISBN: 0-88167-452-4.

DOCUMENT TYPE: Book

FILE SEGMENT: BR; OLD

LANGUAGE: English

AB This text was written by a collection of authors chosen for their expertise in the field of immunopathology which in this book is divided into four subject areas. The first section covered is immunopathologic mechanisms which deals with T-cell and ***antibody*** mediated reactions. The next five chapters individually explore immunopathologic diseases such as ***renal*** and skin diseases, autoantibodies, ***inherited*** and acquired immunodeficiency disorders and ***renal*** allografts. The third-section covers the immunohistochemistry of neoplasia with emphasis on differentiation antigens and tumor ***diagnosis***, cytoskeletal proteins and neuronal tumors, leukemias and the ontogeny of leukocytes, lymphomas, endocrine tumors, soft tissue tumors and tumor stroma. The final section describes and explains such immunopathologic techniques as immunofluorescence, immunoperoxidase, flow cytometry and in situ hybridization. The text is supplemented with micrographs, diagrams, charts, tables and an index.

L65 ANSWER 50 OF 52 MEDLINE

DUPLICATE 20

ACCESSION NUMBER: 89154661 MEDLINE

DOCUMENT NUMBER: 89154661 PubMed ID: 2852640

TITLE: The adenomatous polyp and the hereditary polyposis syndromes.

AUTHOR: Burt R W; Samowitz W S

CORPORATE SOURCE: Department of Internal Medicine, University of Utah, Salt Lake City.

SOURCE: GASTROENTEROLOGY CLINICS OF NORTH AMERICA, (1988 Dec) 17 (4) 657-78. Ref: 81

Journal code: GNA; 8706257. ISSN: 0889-8553.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 198904

ENTRY DATE: Entered STN: 19900306

Last Updated on STN: 19900306

Entered Medline: 19890414

AB Adenomatous polyps are the benign precursors of colorectal adenocarcinoma. Colonic adenomas occur commonly in adults in ***Western*** countries. There is recent evidence that inheritance may play an important role in the etiology of these adenomatous polyps. Colonic adenomatous polyposis (numerous colonic adenomas) is the central feature of several rare ***inherited*** syndromes that give rise to colorectal ***cancer***. There also appears to be a risk of ***gastrointestinal*** and other

malignancies in the rare ***inherited*** syndromes of hamartomatous polyposis.

L65 ANSWER 51 OF 52 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 82029593 EMBASE

DOCUMENT NUMBER: 1982029593

TITLE: The impact of epidemiology upon the ***diagnosis*** and management of gastric disease: The experience of the Hawaii Japanese.

AUTHOR: Grant N.; Stemmermann M.D.

CORPORATE SOURCE: Japan Hawaii Cancer Study, Kuakini Med. Cent., Honolulu, Haw. 96817, United States

SOURCE: Acta Endoscopica, (1981) 11/2 (103-122).

CODEN: AENDD5

COUNTRY: France

DOCUMENT TYPE: Journal

FILE SEGMENT: 017 Public Health, Social Medicine and Epidemiology

006 Internal Medicine

016 Cancer

048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: French

AB Several conditions have been identified as precursors of gastric ***cancer***. The most common of these is intestinal metaplasia (IM) accompanying atrophic antral gastritis (Type B gastritis) in countries at high risk for gastric carcinoma (Japan, Eastern Europe, ***Western*** South America). The risk for this tumor is acquired in youth and persists into old age even if the person migrates away from the high risk area. It has been linked to a diet containing large amounts of salt and nitrate; but lacking in Vitamins C and E. The next most common high risk condition is atrophic gastritis with IM of the oxyntic mucosa accompanying pernicious ***anemia*** (Type A gastritis). This disease is most common in Northern Europe. Carcinoma accompanying intestinal metaplasia is usually intestinal in type; and induction of both IM and ***cancer*** have been attributed to the action of nitroso compounds in the gastric juice. These could be formed by nitrosation of dietary amines, a process that is blocked by Vitamins C and E. Diffuse gastric carcinoma occurs in younger persons who have little or no IM. It is less responsive to environmental changes and is most common in patients with blood Type A. Such persons may have ***inherited*** increased ***susceptibility*** to environmental carcinogens so that a small dose could generate invasive carcinoma with no intermediate stage of IM, as may occur in experimental animals given large doses of nitroso compounds. If gastric carcinoma induction follows repeated mutagenic events, dietary intervention might arrest the process at the level of IM. This could take the form of daily use of Vitamins C and E, and reduced consumption of salt. Recognition of high risk groups might identify persons that might be usefully subjected to periodic endoscopic screening (e.g., every 5 years).

L65 ANSWER 52 OF 52 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 74043308 EMBASE

DOCUMENT NUMBER: 1974043308

TITLE: Diabetes mellitus and thyroid autoimmunity in gonadal dysgenesis.

AUTHOR: Van Campenhout J.; Antaki A.; Rasio E.

CORPORATE SOURCE: Dept. Obstet. Gynecol., Notre Dame Hosp., Montreal, Canada

SOURCE: Obstetrical and Gynecological Survey, (1973) 28/7 (505-506).

CODEN: OGSUA8

DOCUMENT TYPE: Journal
FILE SEGMENT: 010 Obstetrics and Gynecology
022 Human Genetics
007 Pediatrics and Pediatric Surgery
003 Endocrinology
005 General Pathology and Pathological Anatomy
025 Hematology

LANGUAGE: English

AB The authors report a series of 18 patients with endocrine abnormalities of the thyroid and ***pancreatic*** function in association with gonadal dysgenesis. The 4 patients who had a normal 46 XX karyotype also had normal glucose tolerance tests. Only those with an absence of the X chromosome had associated 'possible' autoimmune disease. Autoimmune disease is ***heritable*** and one wonders if the genetic defect responsible for this disease may be in some way related to the genetic defect responsible for abnormal ***ovarian*** development. When treating a patient with gonadal dysgenesis it is important to check carefully for associated serious congenital anomalies, such as coarctation of the aorta and malformations of the urinary tract. Because of the necessity for estrogen therapy, ***uterine*** and ***breast*** ***cancer*** must be routinely screened. Thyroid disease and diabetes must also be checked.

L7 ANSWER 1 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 2001275891 EMBASE
 TITLE: Defects of DNA mismatch repair in human prostate cancer.
 AUTHOR: Chen Y.; Wang J.; Fraig M.M.; Metcalf J.; Turner W.R.;
 Bissada N.K.; Watson D.K.; Schweinfest C.W.
 CORPORATE SOURCE: C.W. Schweinfest, Hollings Cancer Center, Department of
 Pathology, Medical University of South Carolina, 171 Ashley
 Avenue, Charleston, SC 29425, United States.
 schweicw@musc.edu
 SOURCE: Cancer Research, (15 May 2001) 61/10 (4112-4121).
 Refs: 87
 ISSN: 0008-5472 CODEN: CNREA8
 COUNTRY: United States
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 016 Cancer
 022 Human Genetics
 028 Urology and Nephrology
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 AB Loss of mismatch repair (MMR) function leads to the accumulation of errors
 that normally occur during DNA replication, resulting in genetic
 instability. Germ-line mutations of MMR genes in the patients with
 hereditary nonpolyposis colorectal cancer lead to inactivation of MMR
 protein functions, and the defects of MMR are well correlated to the high
 rate of microsatellite instability in their tumors. Previous studies (T.
 Uchida, et al. Oncogene, 10: 1019-1022, 1995; S. Egawa, et al. Cancer
 Res., 55: 2418-2421, 1995; J. M. Cunningham, et al. Cancer Res., 56:
 4475-4482, 1996; X. Gao, et al. Oncogene, 9: 2999-3003, 1994; H. Rohrbach,
 et al. Prostate, 40: 20-27, 1999) have shown that genetic instability
 (chromosomal and microsatellite instability) is detectable in human
 prostate cancer. To elucidate the role of MMR genes in the tumorigenesis
 of prostate cancer, we evaluated the expression of these genes in human
 cancer cell lines and in tumor specimens. Using ***Western*** blot
 analysis, we detected loss among ***MSH2***, ***MLH1***, PMS2, and
 PMS1 proteins in DU145, LNCaP, p69SV40T, M2182, and M12 cells. In
 addition, genomic instability in the prostate cell lines including DU145,
 PC3, LNCaP, p67SV40T, M2182, and M12 was detected by a microsatellite
 mutation assay. Significantly, immunohistochemical analysis of prostatic
 tissue revealed the reduction or absence of MMR protein expression in the
 epithelium of prostate tumor foci compared with normal adjacent prostate
 tissue. In contrast to hereditary nonpolyposis colorectal cancer,
 characterized by defects predominantly in ***MLH1*** and ***MSH2***
 , the samples we examined showed more tumor foci with loss of PMS1 and
 PMS2. PMS1, which is only expressed in the basal cells in normal glands,
 is conspicuously absent in most prostate cancer. From these results, we
 conclude that there are defects of MMR genes in human prostate cancer.

L7 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2001 ACS
 ACCESSION NUMBER: 2000:788458 CAPLUS
 DOCUMENT NUMBER: 135:16144
 TITLE: Immunohistochemical analysis for hMLH1 and hMSH2
 expression in colorectal cancer
 AUTHOR(S): Halling, Kevin C.; Roche, Patrick C.
 CORPORATE SOURCE: Molecular Genetics Laboratory, Mayo Clinic, Rochester,
 MN, USA
 SOURCE: Methods Mol. Med. (2001), 50, 81-86
 CODEN: MMMEFN
 PUBLISHER: Humana Press Inc.

09480389b

DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review with 17 refs. focusing on methods used to study human (h) ***MLH1*** and hMSH2 genes expression.
 REFERENCE COUNT: 17
 REFERENCE(S): (1) Aaltonen, L; Science 1993, V260, P812 CAPLUS
 (2) Aebi, S; Cancer Res 1996, V56, P3087 CAPLUS
 (3) Bubb, V; Oncogene 1996, V12, P2641 CAPLUS
 (4) Cawkwell, L; Gastroenterology 1995, V109, P465 CAPLUS
 (5) Cunningham, J; Cancer Res 1998, V58, P3455 CAPLUS
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2001 ACS
 ACCESSION NUMBER: 2000:493764 CAPLUS
 DOCUMENT NUMBER: 133:117176
 TITLE: Immunoassays to detect diseases or disease susceptibility traits
 INVENTOR(S): Boman, Bruce M.
 PATENT ASSIGNEE(S): Catx, Inc., USA
 SOURCE: PCT Int. Appl., 69 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000042436	A1	20000720	WO 2000-US635	20000111
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG EP 1141726 A1 20011010 EP 2000-903231 20000111 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1999-116247 P 19990114
 WO 2000-US635 W 20000111
 AB Disclosed are ***immunoassay*** methods for the ***diagnosis*** / ***prognosis*** of diseases and disease susceptibility traits assocd. with gene mutations that cause protein truncation or allelic loss. The levels of one or more targeted wild-type proteins expressed by a subject gene or genes are immunol. quantitated in biol. samples. Results indicating that a targeted wild-type protein is not present in an assayed sample, or that approx. 50 % of the normal amt. of such a wild-type protein is present in an assayed sample are considered to be pos. for a mutation in one or both alleles of a subject gene, and correlated with the disease or the disease susceptibility trait assocd. with that mutation or mutations. Normal cells, particularly normal peripheral blood lymphocytes, are preferred biol. samples.
 REFERENCE COUNT: 1
 REFERENCE(S): (1) The John Hopkins University; WO 9109964 A 1991 CAPLUS

L7 ANSWER 4 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 2000326391 EMBASE
 TITLE: ***Msh2*** , ***Mlh1*** , Fhit, p53, Bcl-2, and Bax
 expression in invasive and in Situ squamous cell carcinoma
 of the uterine cervix.
 AUTHOR: Giarnieri E.; Mancini R.; Pisani T.; Alderisio M.;
 Vecchione A.
 CORPORATE SOURCE: A. Vecchione, II Facolta di Medicina, Univ. degli studi
 Roma La Sapienza, Piazza Sassari 3, 00161 Rome, Italy
 SOURCE: Clinical Cancer Research, (2000) 6/9 (3600-3606).
 Refs: 59
 ISSN: 1078-0432 CODEN: CCREF4
 COUNTRY: United States
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 005 General Pathology and Pathological Anatomy
 016 Cancer
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 AB To analyze relevant factors and their effects on neoplastic progression in
 cervical carcinoma, a panel of genetic markers was studied.
 Paraffin-embedded tissue sections were obtained from 37 patients with
 carcinoma of the uterine cervix, 14 noninvasive squamous cell carcinomas
 (NISCCs), and 23 invasive squamous cell carcinomas (ISCCs).
 Immunoreactivity of ***Msh2*** , ***Mlh1*** , Fhit, p53, Bcl-2, and
 Bax proteins was examined by immunohistochemical staining with appropriate
 antibodies . Positive staining of ***Msh2*** was detected in 13
 of 14 (92.9%) NISCCs and in 13 of 23 (56.5%) ISCCs (P < 0.02).
 Mlh1 immunoreactivity was observed in 10 of 14 (71.4%) NISCCs and
 in 8 of 23 (34.8%) ISCCs (P < 0.04.). Overexpression of p53 protein was
 found in 4 of 14 (28.6%) NISCCs and in 16 of 23 (69.6%) ISCCs (P < 0.02).
 Bcl-2 overexpression was detected in 2 of 14 (14.3%) NISCCs and in 15 of
 23 (65.2%) ISCCs (P < 0.003). No significant difference in the two types
 of lesion was found for Bax and Fhit expression. The relationship between
 Mlh1 , ***Msh2*** , and p53 protein expression was significant
 (P < 0.001 and P < 0.001, respectively), as was that between Fhit and Bax
 immunoreactivity (P < 0.02). In conclusion, we consider that altered
 expression of ***Msh2*** , ***Mlh1*** , p53, and Bcl-2 may be a
 critical event during cervical cancer progression, whereas Fhit may be a
 component of a proapoptotic pathway.

L7 ANSWER 5 OF 16 MEDLINE DUPLICATE 1
 ACCESSION NUMBER: 2001072439 MEDLINE
 DOCUMENT NUMBER: 21020488 PubMed ID: 11138465
 TITLE: Characterization of ***MLH1*** and ***MSH2*** DNA
 mismatch repair proteins in cell lines of the NCI
 anticancer drug ***screen*** .
 AUTHOR: Taverna P; Liu L; Hanson A J; Monks A; Gerson S L
 CORPORATE SOURCE: Division of Hematology-Oncology, Department of Medicine and
 Ireland Cancer Center, Case Western Reserve University,
 School of Medicine and University Hospitals of Cleveland,
 BRB-3, 10900 Euclid Avenue, Cleveland, OH 44106-4937, USA.
 SOURCE: CANCER CHEMOTHERAPY AND PHARMACOLOGY, (2000) 46 (6) 507-16.
 Journal code: C9S. ISSN: 0344-5704.
 PUB. COUNTRY: Germany: Germany, Federal Republic of
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200101

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ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010104

AB PURPOSE AND METHODS: The lack of a functional DNA mismatch repair (MMR) pathway has been recognized as a common characteristic of several different types of human cancers due to mutation affecting one of the MMR genes or due to promoter methylation gene silencing. These MMR-deficient cancers are frequently resistant to alkylating agent chemotherapy such as DNA-methylating or platinum-containing compounds. To correlate drug resistance with MMR status in a large panel of human tumor cell lines, we evaluated by ***Western*** blot the cellular levels of the two MMR proteins most commonly mutated in human cancers, ***MLH1*** and ***MSH2***, in the NCI human tumor cell line panel. This panel consists of 60 cell lines distributed among nine different neoplastic diseases. RESULTS: We found that in most of these cell lines both ***MLH1*** and ***MSH2*** were expressed, although at variable levels. Five cell lines (leukemia CCRF-CEM, colon HCT 116 and KM12 and ovarian cancers SK-OV-3 and IGROV-1) showed complete deficiency in ***MLH1*** protein. ***MSH2*** protein was detected in all 57 cell lines studied. Absence of ***MLH1*** protein was always linked to resistance to the methylating chemotherapeutic agent temozolomide. This resistance was independent of cellular levels of O6-alkylguanine DNA alkyltransferase. Based on data available for review in the NCI COMPARE database, cellular levels of ***MLH1*** and ***MSH2*** did not correlate significantly with sensitivity to any standard anticancer drug or with any characterized molecular target already tested against the same panel of cell lines. CONCLUSION: Based on evaluation of 60 tumor cell lines in the NCI anticancer drug ***screen***, ***MLH1*** deficiency was more common than ***MSH2*** deficiency and was always associated with a high degree of temozolomide resistance. These data will enable correlations with other drug sensitivities and molecular targets in the COMPARE database to evaluate linked processes in tumor drug resistance.

L7 ANSWER 6 OF 16 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2000485870 MEDLINE
DOCUMENT NUMBER: 20487343 PubMed ID: 11034530
TITLE: Hereditary breast cancer: high risk genes, genetic testing and clinical implications.
AUTHOR: Hamann U
CORPORATE SOURCE: Deutsches Krebsforschungszentrum, Heidelberg, Germany.
SOURCE: CLINICAL LABORATORY, (2000) 46 (9-10) 447-61. Ref: 146
Journal code: DLI; 9705611. ISSN: 1433-6510.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315

AB About one in eight to ten women living in ***Western*** countries will develop breast cancer during her lifetime and between 5-10% of these cases result from an inherited susceptibility to the disease. Within the past few years, a number of genes associated with a high risk of breast cancer have been identified, including BRCA1, BRCA2, TP53, PTEN, ***MLH1***, ***MSH2***, and STK11. The identification of these genes, together with the rapid advances in molecular genetic analyses, should improve the

diagnosis and therapy of breast cancer. This article reviews the genetic basis of hereditary breast cancer, in particular the contribution of BRCA1 and BRCA2 and discusses the clinical application of this new molecular knowledge with regard to molecular testing, surveillance and prevention in women with a hereditary predisposition to breast cancer.

L7 ANSWER 7 OF 16 MEDLINE DUPLICATE 3

ACCESSION NUMBER: 2000429612 MEDLINE

DOCUMENT NUMBER: 20379086 PubMed ID: 10918209

TITLE: Immunohistochemical detection of mismatch repair gene proteins as a useful tool for the identification of colorectal carcinoma with the mutator phenotype.

AUTHOR: Chaves P; Cruz C; Lage P; Claro I; Cravo M; Leitao C N; Soares J

CORPORATE SOURCE: Department of Pathology, Instituto Portugues de Oncologia de Francisco Gentil, Lisboa, Portugal.

SOURCE: JOURNAL OF PATHOLOGY, (2000 Aug) 191 (4) 355-60.
Journal code: JLB; 0204634. ISSN: 0022-3417.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200009

ENTRY DATE: Entered STN: 20000922
Last Updated on STN: 20000922
Entered Medline: 20000912

AB There are two well-defined pathways for colorectal carcinogenesis, the suppressor and the mutator pathways. The latter is characteristic of hereditary non-polyposis colorectal cancer (HNPCC), but can also be found in a subset of sporadic colorectal cancer (SCC) possessing distinctive clinical and pathological features, namely early age of onset, location in the right colon, poor differentiation, and a predominant mucinous component. This mutator pathway results from inactivation of mismatch repair (MMR) genes, namely ***MSH2*** and ***MLH1***. The aim of this study was to ascertain if abnormal MMR protein gene expression is a good indicator for identifying tumours from the mutator pathway. Seventy-six cases of SCC were studied by immunohistochemistry using two monoclonal mouse ***antibodies*** that react against ***MSH2*** and ***MLH1*** protein gene products. Immunoeexpression was assessed both in tumour and in non-neoplastic, adjacent and distant mucosa. Microsatellite instability (MSI) was detected by evaluating the length of poly(CA) repeated sequences at seven loci, or by the detection of small unstable alleles in a poly(A) repeat - BAT-26. Except for BAT-26, in which only tumour DNA was used, MSI analysis was performed in both tumour and normal mucosal DNA. MSI was classified as high (MSI-H), low (MSI-L) or stable (MSS). Abnormal protein expression was found in 9/76 (12%) tumours. Immunohistochemistry for hmlh1 and hmsh2 detected 75% of MSI-H. There was also a highly significant correlation between the observed immunoeexpression and several clinical and pathological characteristics described as the phenotypic profile of the mutator pathway, such as right-sided location (p=0.003), mucin production (p=0.008), and a peritumoural lymphoid infiltrate (p=0.009). Non-neoplastic adjacent mucosa showed normal hMSH2 expression in all cases, but in ten cases there was no hMLH1 expression in this transitional mucosa, which is known to display an altered mucin pattern and a high proliferative rate. These results demonstrated a good correlation between hMLH1 and hMSH2 gene immunoeexpression and the clinico-pathological features characteristic of the mutator phenotype and support the use of this method as a rapid and efficient way to detect tumours arising from this pathway.

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L7 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:251436 CAPLUS
 DOCUMENT NUMBER: 133:148370
 TITLE: Altered expression of hMLH1 and hMSH2 protein in endometrial carcinomas with microsatellite instability
 AUTHOR(S): Staebler, Annette; Lax, Sigurd F.; Ellenson, Lora Hedrick
 CORPORATE SOURCE: The Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, MD, USA
 SOURCE: Hum. Pathol. (2000), 31(3), 354-358
 CODEN: HPCQA4; ISSN: 0046-8177
 PUBLISHER: W. B. Saunders Co.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Microsatellite instability (MI) has been obsd. in approx. 20% of presumably sporadic cases of uterine endometrioid carcinoma (UEC). A previous mutational anal. of the 4 known DNA mismatch repair genes (hMSH2, hMLH1, hPMS1, and hPMS2) on a small no. of MI-pos. tumors detected mutations in only 2 of 8 cases, both in hMSH2. To further explore the underlying cause of MI in UEC, we analyzed the protein expression of hMSH2 and hMLH1 in UEC of known MI status. Formalin-fixed, paraffin-embedded archival tissue from 21 UECs was analyzed by immunoperoxidase staining with monoclonal ***antibodies*** against hMLH1 and hMSH2 protein. Tumors were evaluated for presence of nuclear staining by 3 investigators. Lack of nuclear hMLH1 staining was found in 7 of 13 carcinomas with MI, but in none of 8 carcinomas without MI (Fischer's exact, 0.018). Lack of nuclear hMSH2 staining was found in 3 of the MI-pos. cases, but none of the MI-neg. cases (not statistically significant). Taken together, lack of nuclear staining of either hMLH1 or hMSH2 was found in 9 of 13 cases with MI and in none of 8 cases without MI (Fischer's exact, 0.005). We conclude that MI in sporadic UEC appears to be assocd. with lack of expression of either hMLH1 or hMSH2, suggesting that inactivation of these genes may be responsible for MI in most MI-pos. sporadic UECs.

REFERENCE COUNT: 29

REFERENCE(S): (1) Aaltonen, L; Science 1993, V260, P812 CAPLUS
 (2) Ahuja, N; Cancer Res 1997, V57, P3370 CAPLUS
 (3) Bronner, C; Nature 1994, V368, P258 CAPLUS
 (4) Burks, R; Oncogene 1994, V9, P1163 CAPLUS
 (5) Cunningham, J; Cancer Res 1998, V58, P3455 CAPLUS
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:656227 CAPLUS
 DOCUMENT NUMBER: 133:250525
 TITLE: ***Prognostic*** relevance of mismatch repair gene mutations in sporadic colorectal carcinoma
 AUTHOR(S): Kruschewski, M.; Noske, A.; Runkel, N.; Berger, G.; Anagnostopoulos, J.; Ringel, J.; Brand, E.; Buhr, H. J.
 CORPORATE SOURCE: Chirurgische Klinik I, Universitätsklinikum Benjamin Franklin, FU Berlin, Berlin, 12203, Germany
 SOURCE: Chir. Forum Exp. Klin. Forsch. (2000) 7-10
 CODEN: CFEKA7; ISSN: 0303-6227
 PUBLISHER: Springer-Verlag
 DOCUMENT TYPE: Journal
 LANGUAGE: German

AB Nineteen % of the mutations in hereditary nonpolyposis colorectal cancer

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are caused by the mismatch repair gene (MMRG) ***MLH1*** or ***MSH2***. MMRG mutation is also obsd. in 15% of sporadic colorectal carcinomas. Studies on tumor characteristics and the ***prognosis*** of this subpopulation have thus far only been performed in patients with microsatellite instability. Since MMRG mutations are not detectable in any tumors with microsatellite instability, the aim of this study was to examine the influence of MMRG on tumor biol. and the course of disease. The study included 127 patients who had undergone curative surgery for a sporadic colorectal carcinoma and a 5-yr postoperative follow-up examn. The following steps were taken: prepn. of 4- to 5-.mu.m sections and immunohistochem. staining with ***antibodies*** against ***MLH1*** or ***MSH2*** (APAAP method), semiquant. anal. by scores with a neg. expression of 0-20% and a pos. expression of 20-100%, and statistical evaluation (.chi.2, Kruskal-Wallis, Kaplan-Meier). 10 Of these patients had a neg. expression of ***MLH1*** and 5 of ***MSH2***, and in 1 case both genes were affected. Differences between ***MLH1***-expressing tumors and those with no expression were found for the pT and pN category but not for grading and angiosis. Lymphangiosis was more frequent in cases with no ***MLH1*** expression (P = 0.018). These tumors were also located mainly in the proximal colon (P = 0.018). Regarding the clin. course, the difference of 72 mo (***MLH1*** neg.) vs. 63 mo (***MLH1*** pos.) in recurrence-free survival was statistically not significant. The tumors with no ***MSH2*** expression did not show any difference in tumor characteristics compared to those with ***MSH2*** expression. Thus, sporadic colorectal carcinomas with no ***MLH1*** expression have a significantly higher lymphangiosis rate and right colon location than tumors with MHL1, whereas this is not detectable in tumors without ***MSH2*** expression. However, a ***prognostic*** relevance for both genes was not obsd. in this patient population. MMRG are thus clin. unsuitable as ***prognostic*** parameters.

REFERENCE COUNT:

4

REFERENCE(S):

- (1) Cawkwell, L; Gut 1999, V45, P409 MEDLINE
- (2) Jin, T; Cancer 1999, V85, P478 CAPLUS
- (3) Maeda, K; International Journal of Oncology 1998, V13, P1147 CAPLUS
- (4) Thibodeau, S; Cancer Research 1998, V58, P1713 CAPLUS

L7 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:113846 CAPLUS

DOCUMENT NUMBER: 130:178314

TITLE: Determining the frequencies of common functional alleles of a gene in a population and therapeutic uses of the information

INVENTOR(S): Murphy, Patricia D.

PATENT ASSIGNEE(S): Oncormed, Inc., USA

SOURCE: PCT Int. Appl., 78 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906598	A2	19990211	WO 1998-US16574	19980804
WO 9906598	A3	19990429		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,

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DK, EE, ES, FI, GB, GE, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG,
UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9887768 A1 19990222 AU 1998-87768 19980804
PRIORITY APPLN. INFO.: US 1997-905772 A 19970804
US 1998-84471 A 19980522
WO 1998-US16574 W 19980804

AB Methods for identifying the frequencies of alleles of a given gene in a population (functional allele profiles) are disclosed. Functional allele profiles comprise the commonly occurring alleles in a population, and the relative frequencies at which such alleles of a given gene occur. Functional allele profiles are useful in treatment and ***diagnosis*** of diseases, for genetic and pharmacogenetic applications and for evaluating the degree to which the gene(s) are under selective pressure. Anal. of sequence polymorphisms at the ***MSH2***, ***MLH1***, and BRCA1 genes in normal populations using PCR to amplify subsequences and sequence anal. is described. The use of allele frequency information to minimize the possibility of adverse effects to drugs is demonstrated by analyzing polymorphisms at the human glucose-6-phosphate dehydrogenase gene. The use of allele frequencies at a no. of oncogenes to est. the likely effectiveness of tamoxifen in chemoprophylaxis of breast cancer is also discussed.

L7 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:96104 CAPLUS
DOCUMENT NUMBER: 130:163999
TITLE: Human MED1 gene encoding DNA repair endonuclease and
diagnosis of susceptibility or predisposition
to cancer
INVENTOR(S): Bellacosa, Alfonso
PATENT ASSIGNEE(S): Fox Chase Cancer Center, USA
SOURCE: PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9904626	A1	19990204	WO 1998-US15828	19980728
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9887613	A1	19990216	AU 1998-87613	19980728
EP 1009230	A1	20000621	EP 1998-939122	19980728
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1997-53936 P 19970728
WO 1998-US15828 W 19980728

AB CDNA and genomic DNA encoding gene MED1 human endonuclease are disclosed. Like other mismatch repair genes which are mutated in certain cancers, MED1, encoding nucleic acids, proteins and ***antibodies*** thereto may be used in genetic or cancer ***screening*** assays. The cDNAs and genes for human and mouse DNA mismatch repair endonuclease are cloned

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and sequenced. The protein contains an N-terminal methyl-CpG-binding domain. The MED1 gene was mapped to human chromosome 3q21. The MED1 enzyme was coimmunoprecipitated with human ***MLH1*** and ***MSH2***. An MED1 mutation resulting in an I358T substitution was found in 10% of hereditary nonpolyposis colorectal cancer patients examined. Another panel of colorectal cancer samples revealed deletion mutations which resulted in premature termination.

REFERENCE COUNT: 2

REFERENCE(S): (1) Hillier; US National Library of Medicine 1996, AA011232
(2) Lewis; Cell 1992, V69, P905 CAPLUS

L7 ANSWER 12 OF 16 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 1999398702 MEDLINE

DOCUMENT NUMBER: 99398702 PubMed ID: 10468602

TITLE: Mechanisms of inactivation of mismatch repair genes in human colorectal cancer cell lines: the predominant role of hMLH1.

AUTHOR: Wheeler J M; Beck N E; Kim H C; Tomlinson I P; Mortensen N J; Bodmer W F

CORPORATE SOURCE: Cancer and Immunogenetics Laboratory, Imperial Cancer Research Fund, Institute of Molecular Medicine, John Radcliffe Hospital, Oxford OX3 9DS, United Kingdom..
Wheelerj@icrf.icnet.uk

SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Aug 31) 96 (18) 10296-301. Journal code: PV3; 7505876. ISSN: 0027-8424.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199910

ENTRY DATE: Entered STN: 19991014
Last Updated on STN: 19991014
Entered Medline: 19991007

AB Fifteen to twenty-five percent of sporadic colorectal carcinomas are replication error (RER) positive. Because the frequency of mutations in the mismatch repair genes (hMLH1 and hMSH2) is low in these tumors, we have investigated the role of mutational inactivation, methylation of the promoter region, and loss of heterozygosity (LOH) as a possible explanation for the mutator phenotype of RER+ colorectal cancer cell lines. Genomic DNA was extracted from a panel of 49 human colorectal cancer cell lines. The RER status was determined by amplification of BAT-26. All exons of hMLH1 and hMSH2 were amplified with the PCR and ***screened*** by using single-strand conformational polymorphism and direct sequencing. The methylation status was ascertained by methylation-specific PCR after bisulfite modification of DNA. ***Western*** blotting for hMLH1 was performed on methylated cell lines before and after the addition of the demethylating agent 5-azacytidine. LOH was sought by GENESCAN analysis of amplified CA repeat markers and indirectly by determining the number of homozygotes in the cell lines and human random controls. Twelve cell lines from ten tumors (24%) were RER+. Hypermethylation of the hMLH1 promoter occurred in five of ten (50%) RER+ tumors, whereas three of thirty-two (6%) RER tumors showed partial methylation. None of the fully methylated cell lines expressed hMLH1, although all reexpressed hMLH1 after treatment with 5-azacytidine. There was no LOH in the RER+ tumors in either hMLH1 or hMSH2. Our results suggest that mutations of hMLH1 together with hypermethylation of the promoter region, but not LOH, are the cause of the mutator phenotype in

the majority (70%) of RER+ tumors.

L7 ANSWER 13 OF 16 MEDLINE
 ACCESSION NUMBER: 1999452157 MEDLINE
 DOCUMENT NUMBER: 99452157 PubMed ID: 10524526
 TITLE: Immunohistochemistry for hMLH1 and hMSH2: a practical test for DNA mismatch repair-deficient tumors.
 AUTHOR: Marcus V A; Madlensky L; Gryfe R; Kim H; So K; Millar A; Temple L K; Hsieh E; Hiruki T; Narod S; Bapat B V; Gallinger S; Redston M
 CORPORATE SOURCE: Department of Pathology, Samuel Lunenfeld Research Institute and Mount Sinai Hospital, Toronto, Canada.
 SOURCE: AMERICAN JOURNAL OF SURGICAL PATHOLOGY, (1999 Oct) 23 (10) 1248-55.
 Journal code: 3YV; 7707904. ISSN: 0147-5185.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199910
 ENTRY DATE: Entered STN: 20000111
 Last Updated on STN: 20000111
 Entered Medline: 19991028

AB Inactivation of deoxyribonucleic acid (DNA) mismatch repair genes, most commonly human mutL homologue 1 (hMLH1) or human mutS homologue 2 (hMSH2), is a recently described alternate pathway in cancer development and progression. The resulting genetic instability is characterized by widespread somatic mutations in tumor DNA, and is termed high-frequency microsatellite instability (MSI-H). Although described in a variety of tumors, mismatch repair deficiency has been studied predominantly in colorectal carcinoma. Most MSI-H colorectal carcinomas are sporadic, but some occur in patients with hereditary nonpolyposis colorectal cancer (HNPCC), and are associated with germline mutations in mismatch repair genes. Until now, the identification of MSI-H cancers has required molecular testing. To evaluate the role of immunohistochemistry as a new ***screening*** tool for mismatch repair-deficient neoplasms, the authors studied the expression of hMLH1 and hMSH2, using commercially available monoclonal ***antibodies***, in 72 formalin-fixed, paraffin-embedded tumors that had been tested previously for microsatellite instability. They compared immunohistochemical patterns of 38 MSI-H neoplasms, including 16 cases from HNPCC patients with known germline mutations in hMLH1 or hMSH2, with 34 neoplasms that did not show microsatellite instability. Thirty-seven of 38 MSI-H neoplasms were predicted to have a mismatch repair gene defect, as demonstrated by the absence of hMLH1 and/or hMSH2 expression. This included correspondence with all 16 cases with germline mutations. All 34 microsatellite-stable cancers had intact staining with both ***antibodies***. These findings clearly demonstrate that immunohistochemistry can discriminate accurately between MSI-H and microsatellite-stable tumors, providing a practical new technique with important clinical and research applications.

L7 ANSWER 14 OF 16 MEDLINE DUPLICATE 5
 ACCESSION NUMBER: 1999065282 MEDLINE
 DOCUMENT NUMBER: 99065282 PubMed ID: 9850030
 TITLE: DNA mismatch repair and O6-alkylguanine-DNA alkyltransferase analysis and response to Temodal in newly ***diagnosed*** malignant glioma.
 AUTHOR: Friedman H S; McLendon R E; Kerby T; Dugan M; Bigner S H; Henry A J; Ashley D M; Krischer J; Lovell S; Rasheed K;

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Marchev F; Seman A J; Cokgor I; Rich J; Stewart E; Colvin O
M; Provenzale J M; Bigner D D; Haglund M M; Friedman A H;
Modrich P L
CORPORATE SOURCE: Department of Surgery, Howard Hughes Medical Institute,
Duke University Medical Center, Durham, NC 27710, USA..
fried003@mc.duke.edu
CONTRACT NUMBER: CA57725 (NCI)
NS20023 (NINDS)
NS30245 (NINDS)
SOURCE: JOURNAL OF CLINICAL ONCOLOGY, (1998 Dec) 16 (12) 3851-7.
Journal code: JCO; 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19990105

AB PURPOSE: We evaluated the response to Temodal (Schering-Plough Research
Institute, Kenilworth, NJ) of patients with newly ***diagnosed***
malignant glioma, as well as the predictive value of quantifying tumor DNA
mismatch repair activity and O6-alkylguanine-DNA alkyltransferase (AGT).
PATIENTS AND METHODS: Thirty-three patients with newly ***diagnosed***
glioblastoma multiforme (GBM) and five patients with newly
diagnosed anaplastic astrocytoma (AA) were treated with Temodal at
a starting dose of 200 mg/m² daily for 5 consecutive days with repeat
dosing every 28 days after the first daily dose. Immunohistochemistry for the
detection of the human DNA mismatch repair proteins ***MSH2*** and
MLH1 and the DNA repair protein AGT was performed with monoclonal
antibodies and characterized with respect to percent positive
staining. RESULTS: Of the 33 patients with GBM, complete responses (CRs)
occurred in three patients, partial responses (PRs) occurred in 14
patients, stable disease (SD) was seen in four patients, and 12 patients
developed progressive disease (PD). Toxicity included infrequent grades 3
and 4 myelosuppression, constipation, nausea, and headache. Thirty tumors
showed greater than 60% cells that stained for ***MSH2*** and
MLH1, with three CRs, 12 PRs, three SDs, and 12 PDs. Eight tumors
showed 60% or less cells that stained with ***antibodies*** to
MSH2 and/or ***MLH1***, with 3 PRs, 3 SDs, and 2 PDs. Eleven
tumors showed 20% or greater cells that stained with an ***antibody***
to AGT, with 1 PR, 2 SDs, and 8 PDs. Twenty-five tumors showed less than
20% cells that stained for AGT, with 3 CRs, 12 PRs, 4 SDs, and 6 PDs.
CONCLUSION: These results suggest that Temodal has activity against newly
diagnosed GBM and AA and warrants continued evaluation of this
agent. Furthermore, pretherapy analysis of tumor DNA mismatch repair and,
particularly, AGT protein expression may identify patients in whom tumors
are resistant to Temodal.

L7 ANSWER 15 OF 16 MEDLINE
ACCESSION NUMBER: 1998203871 MEDLINE
DOCUMENT NUMBER: 98203871 PubMed ID: 9542742
TITLE: Expression of hMSH2 and hMLH1 in colorectal carcinomas with
microsatellite instability.
AUTHOR: Kim H; Piao Z; Kim J W; Choi J S; Kim N K; Lee J M; Park J
H
CORPORATE SOURCE: Department of Pathology, Yonsei University College of
Medicine, Seoul, Korea.. gohk@bora.dacom.co.kr
SOURCE: PATHOLOGY, RESEARCH AND PRACTICE, (1998) 194 (1) 3-9.

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JOURNAL code: PBZ; 7806109. ISSN: 0344-0338.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980609
Last Updated on STN: 19980609
Entered Medline: 19980527

AB Microsatellite instability (MIN) due to defective mismatch repair (MMR) genes has been reported in a subset of sporadic colorectal carcinomas and in the majority of tumors from patients with hereditary nonpolyposis colorectal cancer (HNPCC) syndrome. Among the known MMR genes, hMSH2 and hMLH1 genes are known to be predominantly altered in HNPCC patients and MIN-positive tumors. In this study, we examined MIN and the protein expression pattern of the hMSH2 and hMLH1 by ***Western*** blot and immunohistochemistry from 32 sporadic colorectal carcinomas. MIN was observed in 6 (18%) colorectal carcinomas. Of the 6 MIN-positive tumors, one case showed no expression of either protein, 3 cases showed an absence of hMSH2 protein expression, one case showed an absence of hMLH1 protein expression and one case showed no altered expression of either protein by immunohistochemistry. The decreased expression of the hMSH2 protein in a tumor compared to the normal mucosa was also observed in 5 of the 6 MIN-positive cases by ***Western*** blot analysis. All of the MIN-negative tumors showed expression of both proteins by immunohistochemistry. Thus most of the MIN-positive tumors appear to be directly related to the altered expression of these two genes and can be ***diagnosed*** by the examination of protein expression.

L7 ANSWER 16 OF 16 MEDLINE

ACCESSION NUMBER: 1998060582 MEDLINE
DOCUMENT NUMBER: 98060582 PubMed ID: 9399661
TITLE: Germline hMSH2 and hMLH1 gene mutations in incomplete HNPCC families.
AUTHOR: Wang Q; Desseigne F; Lasset C; Saurin J C; Navarro C; Yagci T; Keser I; Bagci H; Luleci G; Gelen T; Chayvialle J A; Puisieux A; Ozturk M
CORPORATE SOURCE: Laboratoire d'Oncologie Moleculaire, Unite INSERM 453, Centre Leon Berard, Lyon, France.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1997 Dec 10) 73 (6) 831-6.
Journal code: GQU; 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980122
Last Updated on STN: 19990129
Entered Medline: 19980108

AB Hereditary non-polyposis colon cancer (HNPCC) is a common hereditary disease characterized by a predisposition to an early onset of colorectal cancer. The majority of the HNPCC families carry germline mutations of either hMSH2 or hMLH1 genes, whereas germline mutations of hPMS1 and hPMS2 genes have rarely been observed. Almost all of the germline mutations reported so far concern typical HNPCC families. However, there are families that display aggregations of colon cancer even though they do not fulfil all HNPCC criteria (incomplete HNPCC families) as well as sporadic cases of early onset colon cancers that could be related to germline

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mutations of these genes. Therefore, we ***screened*** germline mutations of hMSH2 and hMLH1 genes in 3 groups of patients from France and Turkey: typical HNPCC (n = 3), incomplete HNPCC (n = 9) and young patients without apparent familial history (n = 7). By in vitro synthesis of protein assay, heteroduplex analysis and direct genomic sequencing, we identified 1 family with hMSH2 mutation and 5 families with hMLH1 mutations. Two of the 3 HNPCC families (66%) displayed hMLH1 germline mutations. Interestingly, 4 of 9 families with incomplete HNPCC (44%) also displayed mutations of hMSH2 or hMLH1 genes. In contrast, no germline mutation of these genes was found in 7 young patients. Our results show that germline mutations of hMSH2 and hMLH1 genes contribute to a significant fraction of familial predisposition to colon cancer cases that do not fulfil all ***diagnostic*** criteria of HNPCC.

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FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 17:15:39 ON 01 NOV 2001

L1 1096 S MLH1 AND MSH2
L2 5234551 S DIAGNOS? OR PROGNOS? OR SCREEN?
L3 438 S L1 AND L2
L4 238 DUP REM L3 (200 DUPLICATES REMOVED)
L5 2288750 S IMMUNOASSAY OR ELISA OR WESTERN OR ANTIBOD? OR MAB OR MOAB
L6 26 S L3 AND L5
L7 16 DUP REM L6 (10 DUPLICATES REMOVED)

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CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9825125	A2	19980611	WO 1997-US22430	19971203
WO 9825125	A3	19990805		
W: CA, JP, NO, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1012577	A2	20000628	EP 1997-950877	19971203
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1996-32435 P 19961203
 WO 1997-US22430 W 19971203

AB The present invention relates to the discovery that some alleles of the ataxia-telangiectasia (A-T) gene cause susceptibility to cancer, in particular breast cancer. More specifically, the present invention relates to ***germline*** mutations in the A-T gene and their use in the ***diagnosis*** of predisposition to breast cancer. The invention further relates to ***somatic*** mutations in the A-T gene in human breast cancer and their use in the ***diagnosis*** and ***prognosis*** of human breast cancer. Specifically, one mutation is the nucleotide change ATC .fwdarw. TGAT at base 3245, codon 1082 in exon 24, resulting in a truncation of the protein; a second mutation is a deletion of 150 bp at nucleotides beginning at nucleotide 8269 of codon 2757, leading to the deletion of exon 59 and 50 amino acids in the protein. Addnl. mutations include the deletion of 5 nucleotides beginning at nucleotide 2689 of exon 20, deletion of AA beginning at nucleotide 1402 of exon 12, deletion of GAAA beginning at nucleotide 1216 in exon 10, and the nucleotide change TTT .fwdarw. C at nucleotide 9003 in exon 65. The mutations can be detected by PCR amplification and heteroduplex anal. or in situ hybridization of the mRNA/gene, and immunoblotting or immunocytochem. of the protein product.

L12 ANSWER 14 OF 54 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:785615 CAPLUS
 DOCUMENT NUMBER: 130:34006
 TITLE: Human and mouse multiple tumor suppressor MTS1 and MTS2 genes and their ***diagnostic*** and therapeutic uses in cancer
 INVENTOR(S): Stone, Steven; Jiang, Ping; Kamb, Alexander
 PATENT ASSIGNEE(S): Myriad Genetics Inc., USA
 SOURCE: U.S., 80 pp., Cont.-in-part of U.S. 5,739,027.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 7
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5843756	A	19981201	US 1995-508735	19950728
US 5739027	A	19980414	US 1995-487033	19950607
US 6210949	B1	20010403	US 1998-201139	19981130
PRIORITY APPLN. INFO.:			US 1995-487033	A2 19950607
			US 1994-214582	B2 19940318

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WO 9722689 A1 19970626 WO 1996-US19598 19961217
 W: AL, AM, AU, AZ, BA, BB, BG, BR, CA, CN, CU, CZ, EE, FI, GE, HU,
 IL, IS, JP, KE, KG, KP, KR, LC, LK, LR, LT, LV, MD, MG, MK, MN,
 MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, AM, AZ, BY,
 KG, KZ, MD, RU, TJ, TM
 RW: KE, LS, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR,
 NE, SN, TD, TG

US 5837492 A 19981117 US 1996-639501 19960429
 AU 9714615 A1 19970714 AU 1997-14615 19961217
 JP 2000500985 T2 20000202 JP 1997-522871 19961217
 NO 9802785 A 19980817 NO 1998-2785 19980617

PRIORITY APPLN. INFO.:

US 1995-573779 A 19951218
 US 1995-575359 A 19951220
 US 1995-576559 A 19951221
 US 1996-585391 A 19960111
 US 1996-639501 A 19960429
 WO 1996-US19598 W 19961217

AB Disclosed are methods and materials used to isolate and detect a human breast cancer predisposing gene (BRCA2), some mutant alleles of which cause susceptibility to cancer, in particular breast cancer. More specifically, the invention relates to ***germline*** mutations in the BRCA2 gene and their use in the ***diagnosis*** of predisposition to breast cancer. The present invention further relates to ***somatic*** mutations in the BRCA2 gene in human breast cancer and their use in the ***diagnosis*** and ***prognosis*** of human breast cancer. Addnl., the invention relates to ***somatic*** mutations in the BRCA2 gene in other human cancers and their use in the ***diagnosis*** and ***prognosis*** of human cancers. The invention also relates to the therapy of human cancers which have a mutation in the BRCA2 gene, including gene therapy, protein replacement therapy, and protein mimetics. The invention further relates to the ***screening*** of drugs for cancer therapy. Finally, the invention relates to the ***screening*** of the BRCA2 gene for mutations, which are useful for ***diagnosing*** the predisposition to breast cancer.

L12 ANSWER 24 OF 54 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:254072 CAPLUS

DOCUMENT NUMBER: 126:234427

TITLE: Mono-allelic mutation analysis for identifying
 germline mutations

INVENTOR(S): Vogelstein, Bert; Kinzler, Kenneth W.; Papadopoulos,
 Nickolas

PATENT ASSIGNEE(S): Johns Hopkins University, USA

SOURCE: PCT Int. Appl., 25 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9708341	A1	19970306	WO 1996-US13477	19960823
W:				
AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK,				
EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR,				
LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU,				
SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY,				
KG, KZ, MD, RU, TJ, TM				
RW:				
KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR,				

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IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA
 US 5750352 A 19980512 US 1995-519059 19950823
 CA 2229558 AA 19970306 CA 1996-2229558 19960823
 AU 9669551 A1 19970319 AU 1996-69551 19960823
 EP 847450 A1 19980617 EP 1996-930551 19960823

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, FI

PRIORITY APPLN. INFO.:

US 1995-519059 19950823
 WO 1996-US13477 19960823

AB Mono-allelic mutation anal. (MAMA) is a sensitive and specific
 diagnostic strategy for detection of inherited diseases caused by
 germline mutations based on ***somatic*** cell hybridization.
 Each allele of a human gene involved in the inherited disease is isolated
 in a ***somatic*** cell hybrid. Thus, human peripheral blood
 lymphocytes are fused with rodent (hamster) cell recipients in the
 presence of polyethylene glycol to form human-rodent cell hybrids. The
 presence of microsatellite markers flanking the gene of interest is used
 to confirm the presence of the desired human chromosome in the hybrids.
 The products of the isolated human allele are then obsd. in the absence of
 the other allele of the human. The absence or diminished amts. of the
 protein product detected by ***Western*** blotting indicates the
 presence of a mutation in the gene of interest of the human. The utility
 of this strategy is demonstrated in 2 different hereditary colorectal
 cancer syndromes, one caused by a defective tumor suppressor gene (APC in
 familial adenomatous polyposis) and the other caused by a defective
 mismatch repair gene (hMSH2 in hereditary non-polyposis colorectal
 cancer). MAMA can detect mutations which are impossible to detect with
 std. methods.

L12 ANSWER 25 OF 54 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:805556 CAPLUS

DOCUMENT NUMBER: 128:58317

TITLE: In vivo mutations and polymorphisms in the 17q-linked
 breast and ovarian cancer susceptibility gene BRCA1
 INVENTOR(S): Shattuck-Eidens, Donna M.; Simard, Jacques; Durocher,
 Francine; Emi, Mitsuuru; Nakamura, Yusuke

PATENT ASSIGNEE(S): Myriad Genetics, Inc., USA; Centre de Recherche du
 Chul; Cancer Institute

SOURCE: U.S., 101 pp. Cont.-in-part of U.S. Ser. No. 409,305,
 abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5693473	A	19971202	US 1995-480784	19950607
CA 2196797	AA	19960222	CA 1995-2196797	19950811
WO 9605306	A2	19960222	WO 1995-US10202	19950811
WO 9605306	A3	19960314		
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9533212	A1	19960307	AU 1995-33212	19950811
AU 686004	B2	19980129		

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proteolytic hypersensitivity of this mutant Cro protein. Two of the suppressor substitutions increase the thermal stability of Cro by 12.degree.C to 14.degree.C. These amino acid substitutions affect residues 16 and 26, which are substantially exposed to solvent in the crystal structure of wild-type Cro.

L14 ANSWER 29 OF 29 MEDLINE
ACCESSION NUMBER: 88311011 MEDLINE
DOCUMENT NUMBER: 88311011 PubMed ID: 2900684
TITLE: Cell-specific immuno-probes for the brain of normal and mutant Drosophila melanogaster. I. ***Wildtype*** visual system.
AUTHOR: Buchner E; Bader R; Buchner S; Cox J; Emson P C; Flory E; Heizmann C W; Hemm S; Hofbauer A; Oertel W H
CORPORATE SOURCE: Institut fur Genetik und Mikrobiologie, Universitat Wurzburg, Federal Republic of Germany.
SOURCE: CELL AND TISSUE RESEARCH, (1988 Aug) 253 (2) 357-70. Journal code: CQD; 0417625. ISSN: 0302-766X.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198810
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19950206
Entered Medline: 19881004
AB We have ***screened*** ***antibodies*** for immunocytochemical staining in the optic lobes of the brain of Drosophila melanogaster. Seven polyclonal antisera and five monoclonal ***antibodies*** are described that selectively and reproducibly stain individual cells and/or produce characteristic staining patterns in the neuropile. Such antisera are useful for the cellular characterization of molecular and structural brain defects in visual mutants. In the ***wildtype*** visual system we can at present separately stain the following: the entire complement of columnar "T1" neurons; a small set of presumptive serotonergic neurons; some 3000 cells that contain and synthesize gamma-amino butyric acid (GABA); and three groups of cells that bind ***antibodies*** to Ca2+-binding proteins. In addition, small groups of hitherto unknown tangential cells that send fine arborizations into specific strata of the medulla, and two patterns of characteristic layers in the visual neuropile have been identified by use of monoclonal ***antibodies*** generated following immunization of mice with homogenates of the brain of Drosophila melanogaster.

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(FILE 'HOME' ENTERED AT 17:15:00 ON 01 NOV 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 17:15:39 ON 01 NOV 2001

L1 1096 S MLH1 AND MSH2
L2 5234551 S DIAGNOS? OR PROGNOS? OR SCREEN?
L3 438 S L1 AND L2
L4 238 DUP REM L3 (200 DUPLICATES REMOVED)
L5 2288750 S IMMUNOASSAY OR ELISA OR WESTERN OR ANTIBOD? OR MAB OR MOAB
L6 26 S L3 AND L5
L7 16 DUP REM L6 (10 DUPLICATES REMOVED)
L8 5335 S WILDTYPE

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L9 5149 S GERMLINE AND SOMATIC
L10 0 S L2 AND L5 AND L8 AND L9
L11 92 S L2 AND L5 AND L9
L12 54 DUP REM L11 (38 DUPLICATES REMOVED)
L13 37 S L2 AND L5 AND L8
L14 29 DUP REM L13 (8 DUPLICATES REMOVED)



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Indexing Officer: RCABALLERO - ROSAFI CABALLERO
Team: OIPEBackFileIndexing
Dossier: 09480389

Legal Date: 08-20-2001

No.	Doccode	Number of pages
1	A...	1
2	CLM	1
3	REM	4
4	CLM	8
5	LET.	2

Total number of pages: 16

Remarks:

Order of re-scan issued on